VOLUME 102 • AUGUST 1958 • NUMBER 2

INTERNAL MEDICINE

Dietary Control of Essential Hyperlipemia
Donald S. Amatuzio and Lyle J. Hay

Embryon Truths and Verities Yet in Their Chaos
William B. Bean

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Harold B. Eiber and Isidore Danishefsky

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Habeeb Bacchus

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Hobart A. Reimann

Iron
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A Bibliography of Internal Medicine: Auricular Fibrillation
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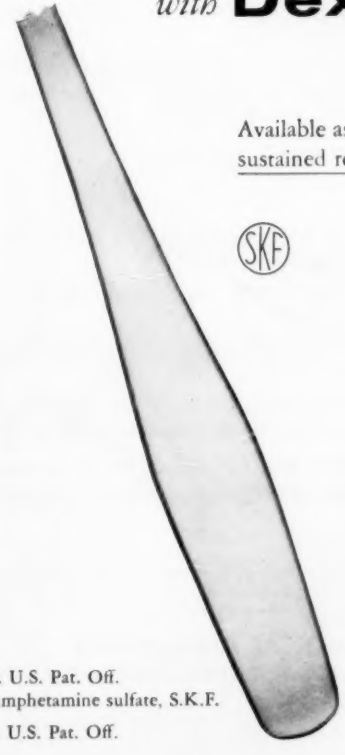

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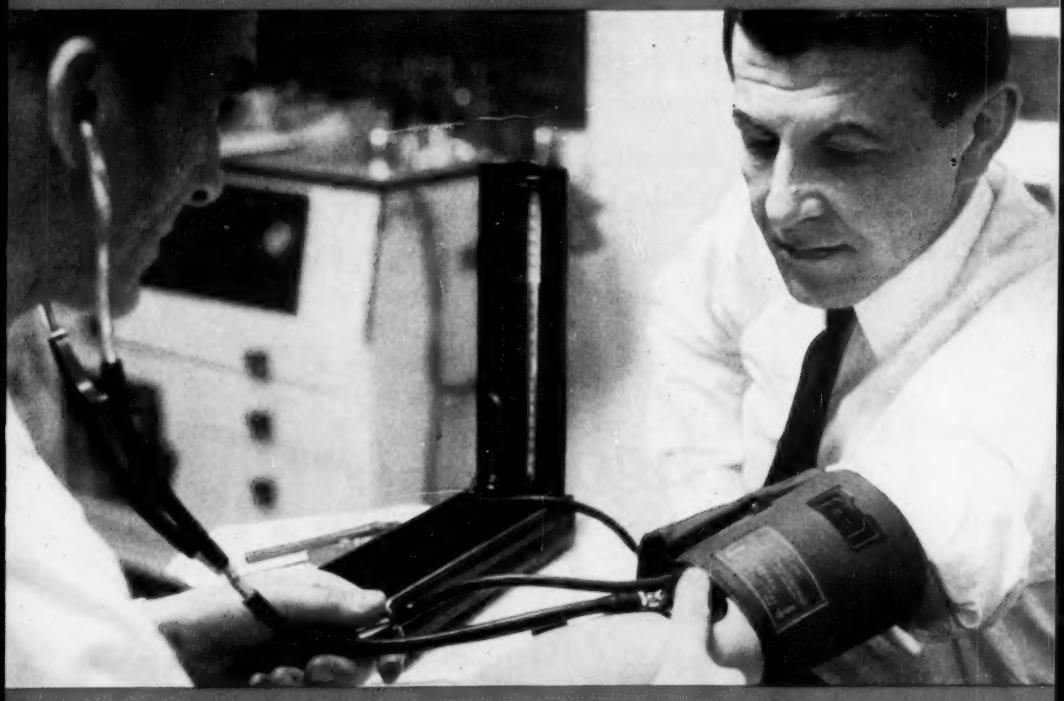

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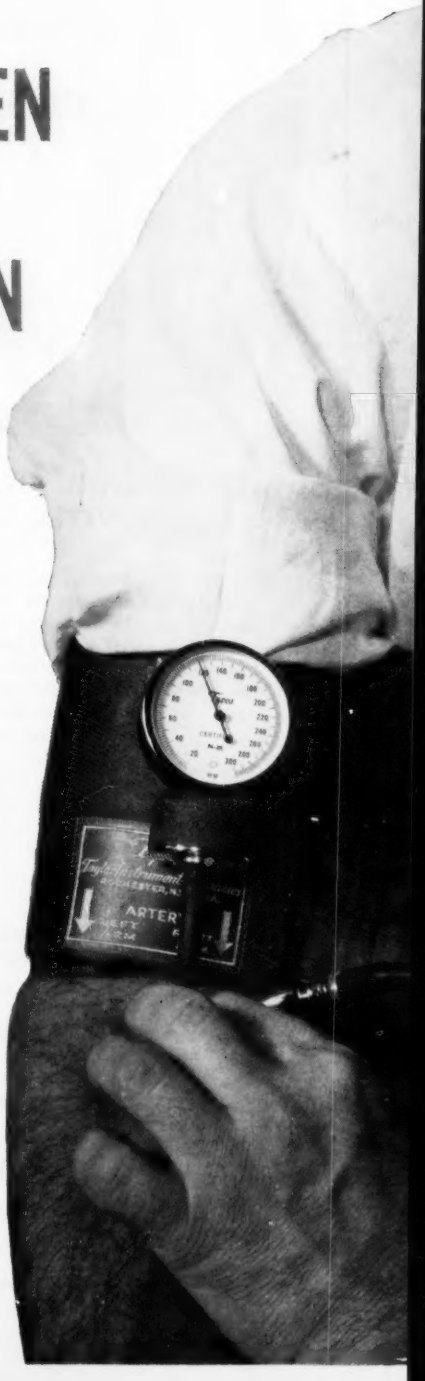

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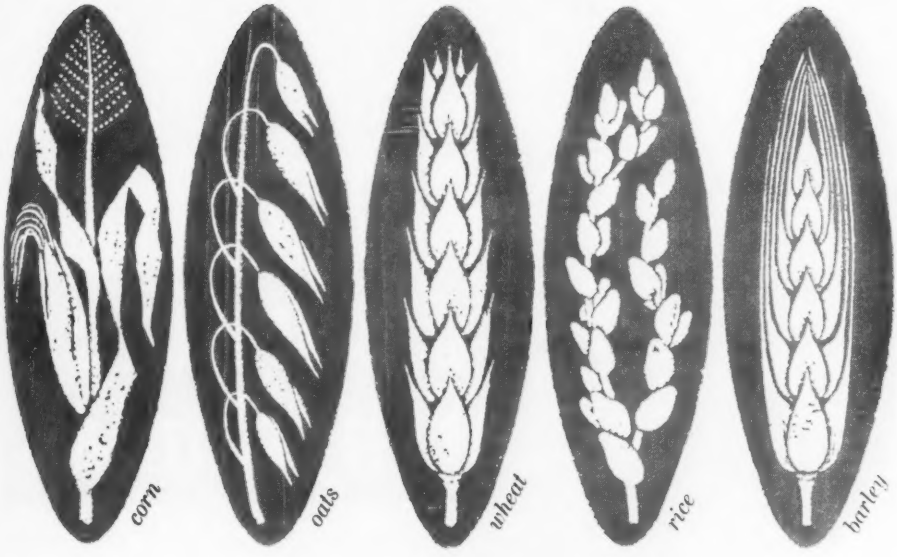

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CALORIES	203	104	83	16
PROTEIN	7.3 gm.	3.1 gm.	4.2 gm.	
FAT	5.3 gm.	0.6 gm.	4.7 gm.*	
CARBOHYDRATE	32.2 gm.	22 gm.	6.0 gm.	4.2 gm.
CALCIUM	0.169 gm.	0.025 gm.	0.144 gm.	
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VITAMIN A	195 I. U.	—	195 I. U.	
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CHOLESTEROL	16.4 mg.	0	16.4 mg.*	

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Bowes, A. deP., and Church, C.F.: Food Values of Portions Commonly Used. 8th ed. Philadelphia: A. deP. Bowes, 1956.
Cereal Institute, Inc.: The Nutritional Contribution of Breakfast Cereals. Chicago: Cereal Institute, Inc., 1956.
Hayes, O. B., and Rose, G. K.: Supplementary Food Composition Table. J. Am. Dietet. A. 33:26, 1957.

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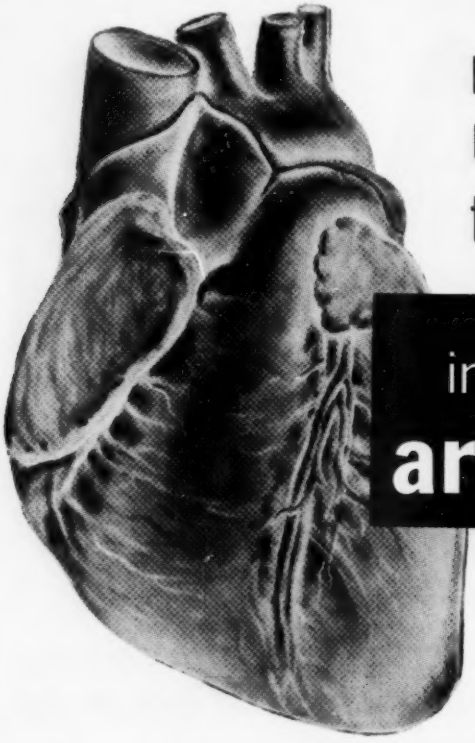

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A.M.A. ARCHIVES OF
INTERNAL MEDICINE

Dietary Control of Essential Hyperlipemia

Effect of Dairy Foods, Phospholipid, Coconut Oil, and Alcohol

DONALD S. AMATUZIO, M.D., and LYLE J. HAY, M.D., Minneapolis

The presence of lipemic serum in fasting persons without associated diseases was first recognized and described as essential hyperlipemia by Burger and Grutz.[1] Symptoms of this disease may be lacking entirely, or there may be weakness, fatigue, angina pectoris, intermittent claudication, and abdominal pain. Physical signs may include xanthomatosis, lipemic retinalis, hepatosplenomegaly, and peripheral vascular insufficiency. The fasting lipemic blood contains increased amounts of neutral fat, phospholipids, and usually cholesterol. Previous case reports have inferred that the disease state is not associated with arteriosclerosis. However, arteriosclerosis is associated with essential hyperlipemia,[2-5] and an effort should be made to correct the elevated blood cholesterol and neutral fat.

With the restriction of fat in the diet the serum lipids in mild cases of essential hyperlipemia generally return to normal values. However, complete clearing of the fasting serum has not always been achieved, and a fat-poor diet is generally not palatable. The purpose of this study is to show the effect of certain dairy foods.* egg phospholipid, coconut oil, and ethyl alcohol on lipemia in fasting patients with essential hyperlipemia who have a normal dietary fat intake. By selectively eliminating the above foodstuffs from the diet it was possible to decrease the blood lipids to normal values in 9 of 12 patients. If either dairy foods, coconut oil, phospholipid, or ethyl alcohol were again added to the diet, a sustained fasting lipemia regularly occurred in these patients.

Submitted for publication Dec. 23, 1957.

Supported by the Minnesota Heart Fund, the Hartford Fund, and the Jay Phillips Research Facilities.

From the Mount Sinai Hospital, Minneapolis, and the Departments of Medicine and Surgery, University of Minnesota.

* Dairy foods include milk, milk products, and eggs.

Material and Method

Nine patients were studied who had previously been recognized as having essential hyperlipemia. No patient had a family history of essential hyperlipemia or hypercholesterolemia. Diabetes mellitus, liver disease, pancreatitis, hypothyroidism, and nephrosis were excluded as the cause of the fasting hyperlipemia. The ages ranged from 7 to 65 years. Two were females, and seven, males. The daily dietary intake included 70 to 90 gm. of fat with a relatively constant caloric intake and excluded dairy foods, phospholipid, coconut oil, and alcohol. Dairy foods or phospholipids were subsequently added to the given diet of two children without any caloric or total fat change per day. Similarly, either ethyl alcohol, coconut oil, or egg phospholipid was added to the diet of seven adults without any caloric or total fat intake change per day. The daily caloric intake of each patient is indicated in the graphs. The patients were studied over a period of 6 to 24 months. Three healthy normal males ages 26 to 38 years were also studied for the individual effect of ethyl alcohol, coconut oil, or egg phospholipid on the serum total esterified fatty acids, the phospholipids, and cholesterol. These men were maintained with a general diet including milk and egg foodstuffs to which 1 oz. of alcohol per day was added for

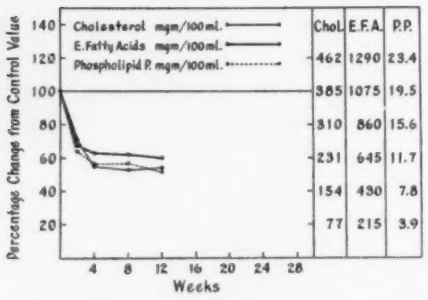

Fig. 1 (Patient 1).—A man, age 59, had coronary occlusion in 1952 and 1953. Hyperlipemia was found in 1952. The diet was 2600 Cal. per day, with 90 gm. of fat, and excluded only alcohol. Weight gain of 2½ lb. in three months.

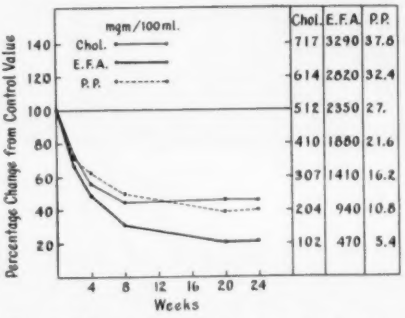

Fig. 2 (Patient 2).—A man, age 63, had coronary occlusion with infarction and diagnosis of essential hyperlipemia five years ago. The diet was 2600 Cal., with 90 gm. of fat per day, and excluded alcohol. The weight of patient increased from 142 to 144 lb. in six months.

one week. Similarly, 35 gm. of egg phospholipid per day and later 1 oz. of coconut oil per day for three weeks were included in the diet. The total esterified blood fatty acids were determined by the method of Baurer.[6] The blood cholesterol and total phospholipids were estimated by the methods of Abell[7] and Youngburg,[8] respectively. The egg phospholipids were prepared by the method of Rhodes.[9] The egg phospholipid was fractionated and found to contain 86% phosphatidyl choline and 14% phosphatidyl ethanolamine.

Graphs were made for each person, showing the effect on the blood lipids of a diet which excluded dairy foods, alcohol, and coconut oil but contained 70 to 90 gm. of fat per day. The individual effect of dairy foods, phospholipid, coconut oil, or alcohol in the diet was then studied after the blood lipids attained a constant baseline and the serum became clear. The ordinates on the left and right in Figures 1 to 9 were designed to permit comparison of the relative and absolute values of the blood lipids, respectively, against time. The addition of specified foodstuffs is indicated by the horizontal bar in the graphs.

Results

Three healthy males received 1 oz. of alcohol per day for one week, 1 oz. of coconut oil per day for three weeks, and later 35 gm. of egg phospholipid per day for three weeks, and these dietary foodstuffs caused no change in the blood lipids during the period of study.

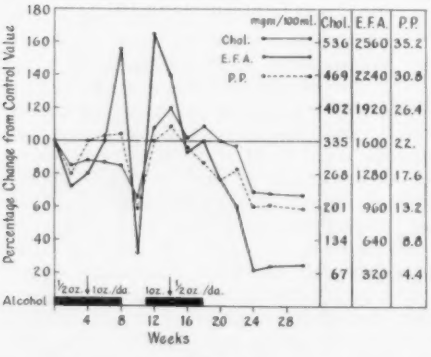

Figure 3

Fig. 3 (Patient 3).—A man, age 42, and asymptomatic. Known essential hyperlipemia for four years. The diet excluded dairy products and coconut oil and contained 2800 Cal., with 90 gm. of fat per day. Note the effect of alcohol on the serum lipids. There was no weight change during the study.

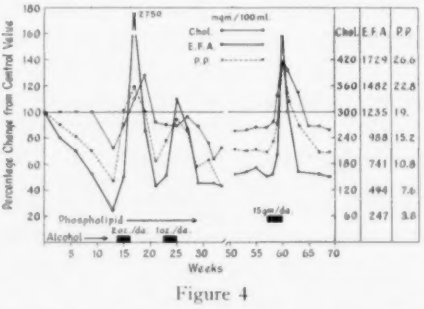

Figure 4

Fig. 4 (Patient 4).—A woman, age 45 had angina pectoris and known essential hyperlipemia for five years. Her diet was 2200 Cal., with 90 gm. of fat per day, excluding dairy products, alcohol, and coconut oil. There was a weight gain of 5 lb. from 129 lb. in the 70 weeks of study. Note effect of adding alcohol or phospholipid.

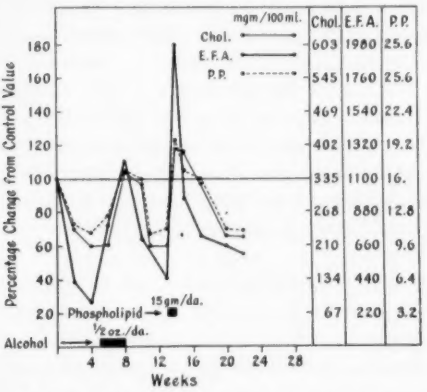

Fig. 5 (Patient 5).—A man, age 51, asymptomatic, was given a 2600 Cal. diet, with 90 gm. of fat per day. His weight remained relatively constant at 176 lb. Note the effect of adding alcohol or phospholipids to the diet.

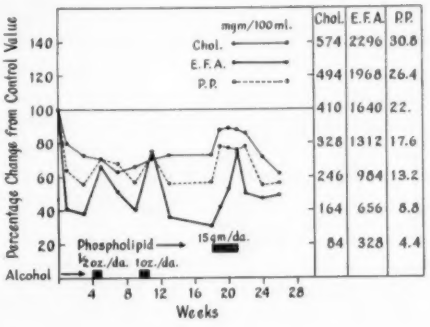

Fig. 6 (Patient 6).—A man, age 63, had coronary occlusion two years previously. He consumed 1 to 2 oz. of whisky per day. He was given a 2600 Cal. diet, excluding dairy products and alcohol. The patient's weight remained at 192 lb. during study. Note the effect of adding alcohol or phospholipid to the diet.

The fasting serum became clear and the blood lipid values, normal in all nine patients within one and three weeks while maintaining a constant caloric intake of 70 to 90 gm. of fat per day and exclusive of dairy foods, coconut oil, and alcohol. The patient's weight either increased or remained relatively constant during the study. The changes in blood lipid values in relation to the above dietary foodstuffs are illustrated for each subject in Figures 1 to 9. The graph ordinates and abscissa have been described above. The relative change of each blood lipid was similar and tended to be parallel.

Effect of Alcohol or Coconut Oil.—With elimination of only alcoholic beverages from Patients 1 and 2 the serum became clear and the blood lipids decreased to the normal range with a diet of 2600 Cal. with 90 gm. of fat per day (Figs. 1 and 2). The diet of Patient 3 excluded dairy foods and coconut oil but not alcohol, and the sustained hyperlipemia did not clear until the alcohol was also eliminated (Fig. 3).

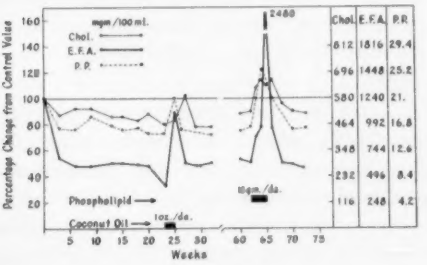

Figure 7

Fig. 7 (Patient 7).—A youth, age 18, had cutaneous xanthomatosis and hyperlipemia for 10 years. He was given a 2800 Cal. diet, with 90 gm. of fat per day exclusive of dairy products. He gained 11 lb. of weight during the time of study. Note the effect of adding coconut oil or phospholipids to the diet.

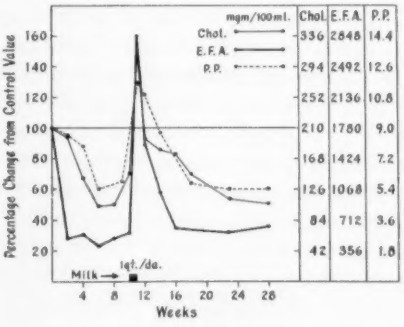

Figure 8

Fig. 8 (Patient 8).—A girl, age 7, was known to have hepatosplenomegaly and essential hyperlipemia for two years. She was given a 2000 Cal. diet, with no dairy products and with 70 gm. fat per day. She gained 13 lb. of weight during the study. Note the effect of elimination and addition of dairy products to the diet.

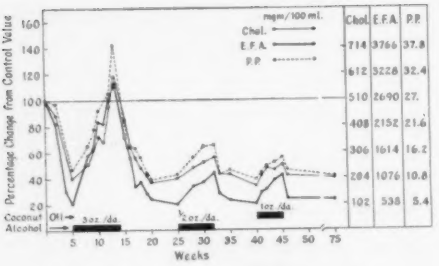

Fig. 9 (Patient 9).—A man, age 55, had coronary and peripheral arteriosclerosis and essential hyperlipemia for seven years. He was given a 2800 Cal. diet, with 90 gm. of fat exclusive of alcohol and dairy products. He gained 10 lb. during the study. The specific effect of adding alcohol or coconut oil should be noted.

After the hyperlipemia cleared and the elevated blood lipids had attained normal and relatively constant values with a diet excluding dairy foods, alcohol, and coconut oil, either alcohol or coconut oil was added. With ½ to 3 oz. of alcohol per day for one to three weeks with an isocaloric intake per day a marked rise of the blood lipids promptly occurred in Patients 3, 4, 5, 6, and 9 (Figs. 3, 4, 5, 6, and 9). When the alcohol was eliminated and an isocaloric intake was maintained, the sustained hyperlipemia cleared and the elevated blood lipids returned to the patients' normal baseline values within two to three weeks.

Similarly, the substitution of 1 oz. of coconut oil per day for two to five weeks without alteration of caloric or fat intake was studied in Patients 7 and 9, respectively. An increase of the blood lipid and a sustained hyperlipemia occurred as illustrated in Figures 7 and 9. After the coconut oil was discontinued and an equivalent fat exchange was added without change in the daily caloric intake, there was clearing of the serum with a return to the subject's normal baseline values within two weeks.

Effect of Milk or Egg Phospholipids.—Milk or egg phospholipid was then studied for the effect on the blood lipids in patients with idiopathic hyperlipemia after the elevated blood lipids and lipemia had decreased and cleared to normal and relatively constant values. After including 1 qt. of milk per day for one week with a removal of a fat exchange in the diet of Patient 8, an increase of the blood lipids with a hyperlipemia occurred (Fig. 8). When the milk was discontinued and an isocaloric diet was maintained, the blood lipids and fasting hyperlipemia gradually returned to the patient's normal baseline values within seven weeks.

Egg phospholipids were added to the diets of Patients 4, 5, 6, and 7 after the patient's serum was clear, with relatively normal lipid baseline values on the standard diet. On substituting 15 gm. of egg phospholipids per day for a fat exchange for one to three weeks without any caloric change per day, a hyperlipemia developed within a week. When the egg phospholipid was eliminated from the diet the blood lipids and hyperlipemia returned to the subject's normal baseline values within two weeks (Figs. 4, 5, 6, and 7).

Comment

Essential hyperlipemia has been described as a hereditary disease state of lipid metabolism. Cases also have been recognized without a hereditary history, after excluding known acquired causes of hyperlipemia. The factors causing a sustained hyperlipemia are not known. A decreased rate of removal of chylomicrons in essential hyperlipemia has been shown,[10] which may be due to inhibitory factors or a defect in lipid metabolism.

After selective elimination of certain foodstuffs, such as dairy foods, coconut oil, and alcohol, from the diet of patients with essential hyperlipemia, the fasting serum became clear with a return of the blood lipids to normal values. The body weight of the patients either remained relatively constant or increased during the study, and there was no endocrine therapy or excessive exercise. A marked decrease in all serum lipid components occurred on eliminating these foodstuffs from the diet. The restriction of other fats is not as important for

the dietary control of the hyperlipemia. It is clear that serum lipids can be altered in many cases of essential hyperlipemia by dietary elimination of certain foodstuffs.

The feeding of coconut oil or dairy foods will cause an elevation of the blood lipids without any increase of the blood triglycerides in patients with hypercholesterolemia.[11,12] These fats are highly saturated and also have a large quantity of short chain fatty acids. The amount of fatty acids of chains of C^{14} or less in dairy products (milk, butter, etc.) and coconut oil is approximately 35% and 65%, respectively.[13] From the present study there is presumptive evidence that these two fats cause a sustained hyperlipemia in patients with essential hyperlipemia.

The addition of alcohol to the diet of the patients in the present study was associated with a sustained hyperlipemia. From previous studies alcohol has been found to affect blood lipids. When ethyl alcohol was included in the diet of dogs, there was an associated increase of the blood cholesterol.[14] Likewise, higher blood cholesterol values were found in habitual drinkers of alcoholic beverages, as compared to those of comparable health and age groups who abstained from alcoholic beverages.[15] This has also been observed in white rats, where twofold to threefold increase of the blood cholesterol and esterified fatty acids occurred after the addition of a small quantity of alcohol per day to the diet.[16]

It is generally accepted that on hydrolysis of fats in the alimentary tract the short-chain fatty acids of 12 carbons and less are transported via the portal circulation to the liver and metabolized by this organ.[17] The fatty acids with less than 12 carbon atoms in the molecules are not stored in animal reserve fat even when fed in the diet.[18] Likewise, the liver is the major site of oxidation of ethyl alcohol to water and acetic acid, which is also a short-chain fatty acid. Because the liver is the site of metabolism of ethyl alcohol and short-chain fatty acids, essential hyperlipemia may represent either a relative metabolic insufficiency or an increased state of lipid metabolism by the liver.

The feeding of a crude phospholipid to normal dogs caused a sustained hyperlipemia and elevated blood lipids. On withdrawal of the phospholipid the blood lipids returned to normal within one week.[21] It was also shown that the feeding of lecithin to a patient with essential hyperlipemia caused an increase in each of the blood lipid components.[22] In the present study, three normal healthy males received 35 gm. of phospholipid per day for three weeks and there was no rise in any of the blood lipids. A hyperlipemia occurred with the feeding of egg phospholipid in four patients with essential hyperlipemia who previously were controlled by diet. The mechanism is obscure but may be due to an inhibitory effect in clearing of the lipemia by absorbed phospholipid.

Summary

Essential hyperlipemia can usually be controlled by selectively eliminating dairy foods, coconut oil, and alcohol, without other restriction in dietary fat in most cases. Certain persons may develop a fasting hyperlipemia due to these foodstuffs. The lipemic fasting serum cleared, and the esterified fatty acids, cholesterol, and phospholipids returned to normal values in seven adults by eliminating alcohol and dairy foods and in two children by restricting only dairy products in the diet. Either dairy foods, phospholipid, coconut oil, or ethyl alcohol caused a hyperlipemia after the serum was clear in essential hyperlipemia.

Nedra Jordan, Audrey Bernstein, and Erma Hanson gave technical help and Eileen Muelken provided dietetic assistance in this study.

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REFERENCES

1. Burger, M., and Grutz, O.: Über Hepatosplenomegale Lipoidose mit xanthomatosen Veränderungen in Haut und Schleimhaut. Arch. Dermat. u. Syph. 166:542, 1932.

2. Malmros, H.; Swahn, B., and Truedsson, E.: Essential Hyperlipaemia, Acta med. scandinav. 14:91, 1954.

3. Soffer, A., and Murray, M.: Prolonged Observations of the Cardiovascular Status in Essential Hyperlipemia, with Special Reference to Serum Lipid Response to Heparin, Circulation 10:255, 1954.

4. Wilkinson, C. F.: Spaced Fat Feeding: A Regime of Management for Familial Hyperlipemia, Ann. Int. Med. 45:674, 1956.

5. Adlersberg, D.: Inborn Errors of Lipid Metabolism: Clinical, Genetic, and Chemical Aspects, A. M. A. Arch. Path. 60:481, 1955.

6. Bauer, F. C., Jr., and Hirsch, E. F.: A New Method for the Colorimetric Determination of the Total Esterified Fatty Acids in Human Sera, Arch. Biochem. 20:242, 1949.

7. Abell, L. L.; Levy, B. B.; Brodie, B. B., and Kendall, F. E.: Simplified Method for Estimation of Total Cholesterol in Serum and Demonstration of Its Specificity, J. Biol. Chem. 195:357, 1952.

8. Youngburg, G. E., and Youngburg, M. V.: Phosphorus Metabolism: I. A System of Blood Phosphorus Analysis, J. Lab. & Clin. Med. 16: 157, 1930.

9. Rhodes, D. N., and Lea, C. H.: Phospholipids 4. On the Composition of Hen's Egg Phospholipid, Biochem. J. 65:526, 1957.

10. Thannhauser, S. J., and Stanley, M. M.: Serum Fat Curves Following Oral Administration of I^{131}-Labeled Neutral Fat to Normal Subjects and Those with Idiopathic Hyperlipemia, Tr. A. Am. Physicians 65:245, 1949.

11. Bronte-Stewart, B.; Antoines, A.; Eales, L., and Brock, J. F.: Effects of Feeding Different Fats on Serum Cholesterol Level, Lancet 1:521, 1956.

12. Ahrens, E. H.; Hirsch, J.; Insull, W.; Tsaltus, T. T.; Blomstrand, R., and Peterson, M. M.: The Influence of Dietary Fats on Serum Lipid Levels in Man, Lancet 1:943, 1957.

13. Hilditch, T. P.: The Chemical Constitution of Natural Fats, New York, John Wiley & Sons, Inc., 1956.

14. Ducceschi, V.: La colesterina del sangue nella intossicazoni per alcool, Arch. fisiol. 13:147, 1914-1915.

15. Ducceschi, V., and Barilari, V.: Sopra la genesi della intossicazone alcoolica: Ricerche sull' uomo, Arch. fisiol. 14:21, 1915-1916.

16. Hay, L. J., and Amatuzio, D. S.: Unpublished data.

17. Geyer, R. P.; Clupman, J., and Stare, F. J.: Oxidation in Vivo of Emulsified Radioactive Trilaurin Administered Intravenously, J. Biol. Chem. 176:1469, 1948.

18. Hilditch, T. P.: Triglyceride Fats in Human Nutrition: Chemical Constitution of Natural Fats, Brit. J. Nutrition 34:347, 1949.

19. Jacobsen, E.: The Metabolism of Ethyl Alcohol, Pharmacol. Rev. 4:107, 1952.

20. Kinard, F. W.; Zimp, J. W., and Aull, J. C., Jr.: Ethanol Metabolism and Liver Enzyme Activity, Proc. Soc. Exper. Biol. & Med. 88:663, 1955.

21. Flock, E. V.; Corwin, W. C., and Bollman, J.: Sustained Hyperlipemia of Dietary Origin in Dogs, Am. J. Physiol. 123:558, 1938.

22. Holt, L. E.; Aylward, F. X., and Timbres, H. G.: Idiopathic Familial Lipemia, Bull. Johns Hopkins Hosp. 65:279, 1939.

Embryon Truths and Verities Yet in Their Chaos

A Discourse on the Unities of Medicine

WILLIAM B. BEAN, M.D., Iowa City

This address is of particular interest because in December, 1927, at Nashville, Dr. William B. Bean's father, the late R. Bennett Bean, an anthropologist and anatomist of some distinction, gave his address as vice president and chairman of Section H, Anthropology, at the American Association for the Advancement of Science. The title was "Stature Throughout the World." It is a happy circumstance that this particular line of family tradition is being carried on in such a distinguished way by this second generation of the Bean family.

P. S. R.

Introduction

Everyone in science has a latent or unrecognized yearning to add a small brick to the edifice of human understanding to enhance man's dignity and make more secure his fragile hold on nature. In this and other matters each of us strives to reach goals of his own choosing, using his own means and whatever skills he may have. Below the surface, unseen forces embedded in us from all our past experience are said to condition our conduct in mysterious ways. Since the goals most of us choose voluntarily are full of vanity and often are chosen unwisely, we may have the wrong objectives. But here fate steps in. We rarely reach our goals. So, if we have set our heart's desire on false ones, failure becomes fortunate.

When I finished medical school I was certain that I wanted no part of academic medicine, but my teachers could not answer some of my simple questions. Sometimes I was amazed at what seemed to be their casual apathy. I had to do my own hunting. Now, years later, I can imagine no other career so worthy or so rewarding as one which combines caring for the sick, teaching, and research. Even the bane of administration is a small price to pay. Everyone must work for a living. Everyone should contribute to the welfare of the community and the welfare of mankind. He is a favorite of the gods who finds that his duty is a pleasure and that he gets rich intellectual and emotional satisfaction in doing what he must do and being paid for it.

I am mindful of the honor done me by my election to this office. I realize that I am expected to deliver an address with some bearing on science, medicine, and their place in our life today. I do not know how I came to be selected, but I am naturally elated. So far as I know no one ever turns down such an honor and obligation, though others must have shared my original impulse to do so. To be honored by one's peers is a challenge which cannot be evaded. I shall talk to some extent of my own work and my special interests in the skin. To feign modesty and protest my inadequacies would be a sorry vote of confidence in those of you who got me into this fix. My task is to captivate my captive audience.

Clinical Versus Laboratory Research

Today the world of medicine and science is very powerful. It is the somewhat sur-

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From the Department of Medicine of the College of Medicine and the University Hospitals of the State University of Iowa.

Chairman's address for the Section on Medical Sciences of the American Association for the Advancement of Science, delivered Dec. 28, 1957, in Indianapolis.

prised recipient of almost too much faith from laymen everywhere. Thus, now more than ever it is urgent that those who transform ideas into action for the betterment of man, those charged with teaching future doctors, and those engaging in clinical research be sound and wise in their policy and practice. I shall look particularly at the relations clinical medicine, practical and investigative, has with the basic sciences, so called. I need not emphasize that my conclusions are provisional, as all interpretations should be. I am interested that with maturity I am losing a proprietary interest in my own opinions. I am uneasy when others try to force them to harden into dogma. Our equity in ideas should be in their continual refreshment and not in their eternal verity, for truth changes as new light alters or obliterates old shadows and silhouettes. Science is ill served by squabbles over priority and intellectual squatters' rights.

In our day no individual man is able to cope with the bewildering complexities in which he is enmeshed. Especially is this true of science and medicine. We have tried in two ways to escape to a tenable position to survey the terrain. These are by the specialization of knowledge and by the erection of institutions. Indeed, institutions themselves foster specialization by division of labor. Thus trying to solve complexity we have achieved isolation. The corpus of knowledge keeps breaking into ever small subdivisions tended by workers not only inarticulate in other fields but largely unaware of them. Analysis, the partition of knowledge and its advance on a multitude of separate fronts has not seen the complementary development of synthesis, the weaving of what often seems to be a tangle of old and odd threads into a new cloth with a fresh pattern.

Dermatology

In talking about the sciences, basic science and its sometimes belittled mother, clinical science, my excursions into the realm staked out by dermatologists give me ample reason to seek out certain muted chords, variations on the theme of *the unities of medicine*. And this is appropriate, since our theme at this meeting is the skin—a covering common to all and a fitting topic for discussion.

The specialty of dermatology, not yet a hundred years old, arose when man really began to look at himself and then think about what he saw. Its pioneers explored and catalogued. They mapped unknown land. As biologists they were natural historians of disease. Being educated in the classics, they erected a formidable list of Latin and Greek names for warts, pimples, poxes, and rashes. At times the practitioners of the art of dermatology were guilty all unwittingly of that ancient abdication from reason, the heresy that to name was to know. Physicians always must be alert to keep in mind the fact that giving a name or making a diagnosis is the beginning and not the end of wisdom or even of learning. The act of naming a disease has never quite escaped from the ancient priest-physician's belief that naming gave control. Thus, before dermatology was fairly launched as a special interest in medicine, it was nearly sunk by a naive faith in nosology and a system of nomenclature, sound in principle but holding the danger that it become deified in a static iconography not recognized as ultimately false in that it was fixed. My former chief, the late Dr. Blankenhorn, a superb clinical teacher, used to say that he shared the dermatologists confusion but not their terminology, a statement fortunately no longer justifiable since dermatology has emerged as a clinical science.

The next move was the unhappy separation of dermatology into a specialty apart from general medicine. This looks innocent enough. At first it is, because individual specialists were physicians whose talent or taste led them into a particluar field—in this case, dermatology. But as a clinical specialty grows it wants status. It needs status. Its devotees band together. They form societies,

publish journals, and quarry out a block of time in the curriculum of medical schools. At length a hierarchy of elite members determines who shall be allowed to call himself a dermatologist. It *pre*scribes certain final conditions of study and experience, *pro*scribes others and admiringly sets a halo on its own head. Eventually a self-perpetuating board of censors, beholden to no medical college, without charter as university, determines rigid requirements for study, qualifications for admissions to the examinations, and repeatedly fluctuating rules for certification. Thus the heavy hand of the stereotype is raised to stifle originality.

The loss to general medicine is to forget to study the skin. This loss is great or only moderate, depending on whether departmentalization in teaching, research, and practice separates not only individual persons but the free interchange of ideas. The loss to dermatology is the tendency to see medicine as skin deep or not even skin deep but as an isolated problem, a bit of churning flotsam to take to the laboratory rather than part of the bewildering complexity of man. In disease and health man cannot be understood piecemeal, even if he has to be studied that way.

But the wisest practitioners of dermatology and medicine have never lost sight of the essential connection of the two in the larger unity of general medicine. The danger has been rather that those who have narrowed their focus to a particular aspect of structure, function, or disease of the skin will lose perspective or that those in basic science have something of importance for clinical medicine but knowing little medicine fail to establish contact. Basic science is essential, for we cannot expect to advance learning without using to the full skills existing only in the laboratory. Indeed, help often comes unexpectedly from work along very different lines from those we are pursuing.

Complexity—the Plight and a Solution

Physicians who are teachers have known for some time that neither all the facts nor all the skills can be learned by undergraduate students, not even in the long later years of apprenticeship to qualify as specialist. We have not resolved the problem that while *ultra*specialization is essential in most research, it is bad for teaching, deadening to the practice of medicine, and may even be fatal to the patient. Solution may be impossible. But we cherish hope that man will not be lost in a sea of confusion, utterly overwhelmed by the great surfeit of undigested facts, shipwrecked by an overweight of knowledge.

Two methods have been suggested to find a way out of our increasing confusion in practical medicine. At one extreme is the plan to emphasize laboratory research further and separate it from practice and teaching. The medical school of the future is seen as a cluster of research institutes to which the hospital-clinic is attached as a necessary but scarcely honored appendage. Or a great hospital is built expressly to study disease, not to heal the sick. Clinical medicine becomes a parasite on basic research. At the other extreme, we have individual clinical teachers and practitioners who personally have had training in chemistry, physiology, physics, or other fields and who do with their own hands the researches suggested by the puzzling troubles of sick patients. Too often they are old before their training is completed and they can get on with their work. Nevertheless, this seems the best though the most costly solution. Midway between, we have Ph.D.'s with a home base in a clinical department. They are uneasy about losing identity with their primary group. They may have joint appointments in biochemistry and medicine or dermatology. Or collaborative effort goes forward as a true partnership. Too often the clinician may seem to, or actually try to, exploit someone in basic science to do his work for him. No form of research which employs slave labor can flourish. Slave and

master alike decay. But those in basic science must recognize the essential role of clinical research as well as its profound difficulty and vexing frustrations. Lacking the neat precision of the laboratory, it shares the same rigorous disciplines, scepticism, and critique.

Poor contact between basic science and clinical medicine is illustrated in the long lag from the early clinical knowledge of antiscorbutic foods, and of the circumstances under which scurvy appeared, to the final isolation and synthesis of ascorbic acid. Just over 200 years ago, James Lind summarized his extensive medical experiences in the British Navy in his treatise entitled "The Scurvy." He defined the disease, expounded its cause, described its cure, and illustrated its prevention. As an example of the ponderous movement of bureaucracy the Lords of the British Admiralty adopted Lind's recommendations as official doctrine for the Royal Navy at about the time of his death, after a lapse of only 40 years. But an even more ponderous delay occurred in the 125 *more* years which were needed before students of chemistry and physiology finally got around to the isolation and synthesis of ascorbic acid. During the last two decades, many in vitro functions of ascorbic acid have been clarified but not the mechanism of its function in man.

Another delay in understanding medical problems, worked out from the solitary point of view of a single laboratory specialty, is illustrated by the fact that the clinical diagnosis and understanding of myocardial infarction, ancient history to the pathologist, was not made until fairly recent times. To be sure, the electrocardiograph was very helpful, but it could not be applied until clinicians, led by Herrick, Dock, and others, recognized that infarction of the heart was not invariably fatal. Many more examples could be adduced to suggest at least a partly negative answer to Trotter's searching question, "Has the intellect a function?"

Thus, the past saw much reluctance of those in basic science to tackle the problems of clinical medicine. Under the impact of laboratory research, change began. It has continued with accelerated speed. The trend of neglect has been reversed completely in a few spots. Laboratory scientists have outstripped the clinician in knowledge of certain biochemical problems relating to nutrition. We are in the uneasy situation of having vitamins whose function in man is not known and must be inferred by extrapolation from known or suspected biological functions in lower animals and from in vitro studies.

Let us then consider some of the differences between laboratory and clinical research, recognizing that no fixed line separates them. There *are* real differences. Among the paradoxes which may confound an easy understanding of the relations of laboratory science and clinical science is the problem of normality, individuality, and the textbook picture of some specific disease. The more closely science in the laboratory approaches complete mathematical specification, the further molecular and physical systems must be abstracted from the actuality of their infinitely more complex relationships in a living man. Thus, as science becomes more exact it tends to lose contact with medical reality, or at least it runs that risk. One cannot escape the view that laboratory science is not always on guard lest, impelled by techniques and constrained by apparatus, it give an ironic answer to John Hunter's impetuous questions: "Why think? Why not try the experiment?"

Whereas clinical science may be depreciated because of its inherent vagueness and complexity, laboratory science as it explores deeper and deeper takes on a cast of unreality which always skirts the haunting possibility that it is beguiling itself by reproducible artifacts. If we refuse to grant significance to anything which cannot be proved in a laboratory, we have gone a long way toward convincing ourselves of the truth of the ancient charge against Socrates

that he was trying to prove that the lesser is the greater thing.

The Kinds of Clinical Science

The study of patients with lesions of the skin may be approached as descriptive natural history. Knowledge of natural history enables us to identify a disease or lesion, to infer its cause, to predict its probable course, and to forecast the outcome. Experience and what can be taught of others' experience enable us to identify and then study the phenomena of disease, their probable interrelationships, and the consequences. Disease may be defined as the reaction of the body to some injurious force or forces which may not always be known. From the train of events observed in a series of persons sick in the same way, we generalize what is called a textbook picture, a useful figment but still a figment, since no patient will have all his signs or symptoms at the dead center of an average and keep them there. We must recognize disease in this way to estimate severity, to judge prognosis, and to evaluate treatment. No matter how clumsy this tool may be, it is the only one we have in clinical medicine. If we scorn it for the cleaner-cutting edges of speculation and arbitrary systems we mix weed and wheat in neat but unusable bundles.

The other major form of clinical research is mechanistic in intent and mechanical in procedure. It has as its function the study of how things work. Bleeding, pain, itching, and imbalances in the acid-base metabolism are its subject material and only incidentally the study of disease and perforce but sometimes reluctantly of the sick man. Its method is experiment; its guide, technique, its means, an instrument. It has many notable exponents and was brought into a noble state of fruition by such people as Mackenzie and Thomas Lewis in England and Soma Weiss in this country. Its contributions are far too numerous to mention. Much of this symposium on skin disease exemplifies it. Its danger is that it becomes too selective, views with oil immersion before scouting with lower powers, and, if not eternally vigilant, does research on such a small fraction of the phenomenon that it shares the danger of other laboratory research by becoming an abstraction and losing reality.

There are different kinds of clinical observation. I shall illustrate some of them. Clinical observation depends on training, on active curiosity, and on the ability to see the importance of the unexpected or to recognize the unusual when one is diligently searching out the usual, the commonplace, or the anticipated phenomena of an experiment. In fact, the ability to distinguish a new phenomenon or to recognize certain obvious aspects of reality is so rare that it takes on some of the quality of creative genius.

Looked at from another point of view, clinical research finds room for employment of at least three kinds of activity which have no necessary rank order of excellence. The most primitive type of observation is that which everyone practices every day. By it we identify objects we see. We are enabled to thread our way through the maze of traffic on a busy street, preferably with the help of traffic lights and traffic policemen. It helps us identify the bark of our dog at night and to know by sound of voice or step members of our family and close associates. Carried slightly further along, it is the method by which practitioners a hundred years ago and, of course, today diagnose and prognosticate. It sees the splinter hemorrhage and the small purpuric lesion at a time when more casual observation or an untrained person would miss them. It knows when to mistrust a laboratory report as obviously in error or probably wrong. As it is applied to the art of medicine it is called clinical hunch, or intuition, because it depends on economy of effort which takes many mental steps unconsciously to arrive quickly at the proper destination over unseen stepping stones. Though it may be looked upon by the novice as almost magical, there is nothing

magical about it. It is simply the sifting of essential from spurious which occurs so rapidly that conscious intellectual effort cannot be seen to have been part of it. A skilled physician thus practicing may not be able to explain the devious paths he took and how he seized on the cardinal features almost in an instant.

This kind of observation is hardly research. It takes the experience of the person and blends it with what he has learned from others. It is not likely to find new discoveries, either. It is impossible to communicate in its entirety and must be built up by each physician for himself, but clinical practice without it is null and void, despite laboratory brilliance and technical virtuosity.

A second type of clinical observation comes close to approaching the highest creative intellectual activity, in which imagination fashions art or discovery. Pasteur had the imaginative and intuitive approach. Some new and luminous truth apparently arises spontaneously but usually after intensive thought and frequently after deep meditation, or it may come from no apparent stimulus or obvious connection with any conscious mental activity. As examples, one can cite Fleming's realization of the possible significance of the troublesome inhibition by the growth of a mold of his special bacterial friends, the luminous ideas which inspired Castle's work on the pathogenesis of pernicious anemia, Hench's observations of pregnancy and liver disease as unexpected relievers of the symptoms of rheumatoid arthritis, and Gregg's recognition of the association between German measles early in pregnancy and the occurrence in the offspring of congenital deformities. As Spence said:

> This kind of clinical observation for which I can find no suitable name is one of the most scintillating starting points of scientific research, but we cannot order it or command it. The best we can do is to recognize its possibility in the sensitive few, and to prevent its inhibition by too much teaching, its submersion by too much dogma, and its extinction by too much ritual even though it might be the ritual of research.

The third form of clinical observation is perhaps more clearly recognized as Lewis' clinical science or our clinical research and clinical investigation. It requires, first of all, (1) an idea based on (2) observation. This idea brings to mind (3) a question. The question must be formulated precisely with these things in mind: (4) that it is worth asking, (5) that it has not already been answered by someone else, and (6) that in the precise form in which it is asked it will provide an answer which says yes, no, or how much. Then, and this is often overlooked, (7) it must be asked by someone who has the qualities of intellect and endurance to do the actual work necessary to get an answer and, finally, the answer must be able to be (8) perceived, (9) understood, and (10) communicated, not necessarily in deathless prose but in something besides a series of tables and charts. Its purpose is to get new knowledge or to make more sense out of old knowledge by a new alignment of facts already known.

The capacity to reach excellence in these forms of observation depends on several qualities: First of all, curiosity. Each must retain some of the boundless excitement, the glow of wonder, and the incorrigible persistence of the child as he begins to find his way around in a new world. Unfortunately, this curiosity may be stifled by our system of education, with its great emphasis on memorizing masses of details. The next qualification is skepticism, which leads to a critical view of all the phases of observation, experimentation, interpretation, and the drawing of conclusions, and a third qualification includes some of the elements of a prophet, which at its highest approaches the wisdom of Galileo, who believed that phenomena could be ordered into "natural law gradually attainable half by discovery and half by creation."

Vascular Spiders

I shall talk briefly about vascular spiders and other vascular lesions of the skin. When I was an intern at Johns Hopkins, spiders

with liver disease were accepted but no one could tell me why. At Harvard I could get no help from Minot, Castle, Weiss, and other great men of the Thorndike. In Cincinnati, Blankenhorn encouraged Donald Forster, Morton Hamburger, and me to go on with our study. Cirrhosis was plentiful. I saw dozens of patients with spiders. Serious doctors thought this a quaint but harmless passion. Before long I was called to see some of the residents' wives, who got spiders while pregnant, had no liver disease, and lost the spiders after pregnancy. After reading Walsh and Becker's paper on spiders and palmar erythema, I found that I had been seeing and writing notes about curiously red hands without registering anything. At length I had collected systematic notes on 250 persons with spiders, searched for reports buried here and there in medical writings, and meditated upon the strange association of spiders and palmar erythema with chronic liver disease and with normal pregnancy. Medicine had become so specialized that no one else had been aware of the eruption of spiders in both advancing liver disease and advancing pregnancy. I suggested that estrogenic hormones, natural in pregnancy, accumulating in excess in disease of the liver might cause this change in the blood vessels of the skin as well as produce the long-known effect on endometrial and myometrial spiral arteries. Giving estrogens to a few subjects encouraged me to believe that the idea was valid.

A time for reflection, speculation, writing, and rewriting came with a four-year turn in the Army, when I was detached from clinical work. A monograph was produced which I thought would sink into the vast ocean of medical literature without a splash. The effect was pleasantly different. Hepatitis, not the confidently expected influenza, was the epidemic of World War II. Despite my detailed description of the arterial spider, and hereditary hemorrhagic telangiectasia, mistakes are made repeatedly. Many useful signs are missed. Others are misconstrued. Since the patient cannot be examined by a laboratory, errors may arise from lack of effort and of knowledge. In recent years I have described in detail many of the hitherto uncodified features of a variety of related lesions. I will take you for a brief tour through my gallery.

Here the main clinical features, the significance, and some aspects of pathogenesis of several vascular lesions of the skin were illustrated by slides and movies. The detailed studies upon which this discussion rested have been reported in a series of papers and mongraphs listed in the references, where may be found a discussion of the writings and ideas of other investigators too.[1-16]

The Discipline of Method

I have evolved a plan for the systematic collection of data on vascular lesions of the skin. It seems so simple as to be scarcely worth bothering you with, but such a systematic study is too much trouble or too drab for most physicians, dermatologists, or internists. Somewhat surprisingly, I have become an exponent of what used to be called, with grace and feeling, natural philosophy. I have found it convenient to collect and record information along these lines:

1. Decide what kind of a lesion is to be observed and evolve a careful description and definition of it. I now keep notes on several dozen vascular lesions and related marks in my patients.
2. Determine and record the topography related to the microcosmic geophysical anatomy of skin and mucous membrane.
3. Is there a relationship to sex?
4. Is there a relationship to age?
5. Is there a connection with disease or other states, such as pregnancy, or is it a parameter of health?
6. Do such factors as race, complexion, skin color, or occupation have any bearing on the problem?
7. Are there temporal factors of clock or calendar related to onset, growth, course, ultimate fate, changes, and circumstances of coming or going of a lesion?
8. Analyze the gross and microscopic morphology of the lesion.

9. Evaluate geographical and environmental factors.

10. Historical aspects may be left conveniently for later, lest prejudice or established error influence one too much. Since most lesions will be known already, we are not really beginning from virginal ignorance.

11. Employ the methods of chemistry, physiology, and any other appropriate science to explore leads which are uncovered in the clinical study. This may be the work of a few weeks or a lifetime.

12. Go back to patients and verify the products of laboratory research.

13. Communicate useful findings and employ them in practice and teaching.

14. If possible integrate the whole and synthesize the knowledge into practical wisdom and erect hypotheses, not as a corral to keep unbroken horses in permanent stockade but as a scaffolding to be taken down when a particular part of the structure of science is built solid.

As I have continued to expand my observations, I have become aware of two things. One is the profound difficulty of seeing perceptively what is there. Loss of intellectual energy is the price we pay for strict and complete concentration. We live in a day of distraction, when only the very persistent or the truly great can sacrifice that part of themselves which is used up with complete attention. The process resembles on a small scale what happens to a bee when it stings. It is too painful for most of us to try.

The second may be part of the humility arising from experience. Fortunately it comes often to those whose life is spent in teaching and practicing medicine. Progress is too fast for us. Medicine has made truly splendid advances. These are being spread before you at this annual meeting in impressive splendor. We expect such excellence to be so routine that we hardly praise outstanding work. But those of us who daily confront patients who have troubles large or small, banal or fatal—how little do we know of the minute temporal anatomy of disease and its causes, ecology, and precise unfolding in John Smith, a single unique person, who is changing before our eyes as he is influenced by all the myriad variables of seed, soil, fertilizer, and climate. How rare it is for a physician, resident, or undergraduate student to trace entirely through even one night watch the kaleidoscopic movements of all the little secrets of a sick man and his disease. And how much rarer is such a vigil, measured in months, years, or a lifetime, as a patient shifts from work, to home, to doctor's office, to hospital, out again, and to the cure or fatal end of his disease. We know that the textbook picture, at best a matter of averages, never suits a given patient in all particulars or for long. How rarely can we pinpoint the secular trends with precision or generalize clearly data collected by diligence. How few of us are aware of all the turbulent variables as we pursue our clues amidst a network of shifting, bending, and seemingly elastic coordinates. This is no idle demonstration at the wailing wall, and I hope my plea for excellence and work demands no more than we can evoke of diligence taught by discipline to become clinical wisdom. If we cannot realize these objectives, we might as well mechanize medicine and put it in the hands of engineers and bureaucrats, who suspect that they can make it more efficient and pretty it up by automation. No. Everyone in clinical practice, if he has any compassion and any perception, knows that too often he is at the mercy of uncertainty. And this lack of certainty is born of ignorance about the knowable. It is the failure to observe rather than the inaccessability of facts. It cannot come from laboratory research, and without it the spectacular know-how of the laboratory may lead to nothing more than abstractions—*bombinans in vacuo*. My thesis is that we will never improve the situation unless we can attract into the arena of the sick dedicated workers who will observe attentively, collect data, and trace to their best capacity things obviously important and obviously unimportant. Until the small shoals as well as the giant headlands of disease have been mapped, we shall move with the halt, the lame, and the blind in our recurrent shipwrecks.

Conclusion

Well, as happens on any journey into a new land, I started out confidently enough in familiar territory and made good progress for a time. Soon the trail faded out. I stumbled on. Perhaps I was not even as sure of where I was as Daniel Boone, who, when asked late in life if he had ever been lost in the wilderness, pondered a bit and answered, "No, but once I was bewildered for three days." With overmuch effort I have arrived at some simple platitudes, axioms, I believe, for anyone concerned with mankind as a biological phenomenon, and something more—men and women—the persons he knows and the patients he studies and treats.

I maintain that science and medicine cannot achieve their best purpose until clinical science regains its status as the mother of sciences. This is not to be done at the expense of laboratory research or even in competition with it. Clinical and laboratory science must be partners of equal stature. Collaborative research, a team of horses yoked together, may not win any Derbies but might win some chariot races. If we continue emphasis on projects, piece work, equipment, and techniques at the expense of clinical work, medicine will suffer. Laboratory work must not be directed by machines, reducing each problem to an artificial fiction with only one variable, for then it is separated so far from reality that its numbers are mere abstractions. Clinical medicine must concentrate on the particular, watching many things at once, frustrated by variables out of control and many not even known, limited by what it may do in manipulative experiment but alert to make the most of Nature's experiments which no laboratory can duplicate. It must guard against diffuseness, premature generalization, and the conception of biological truth as fixed. For it is only by warm cooperation of men in the various special disciplines, such as chemistry, physiology, physics, and pathology, with clinicians that greater biology will lead to a better understanding of man. I trust that at least the theme of my discourse is in keeping with Sir Thomas Browne's wonderful words of old from Christian Morals, "Let thy studies be free as thy thoughts and contemplations: but fly not only upon the wings of imagination; join sense into reason, and experiment unto speculation, and so give life unto embryon truths, and verities yet in their chaos."

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REFERENCES

1. Bean, W. B.: A Note on the Development of Cutaneous Arterial "Spiders" and Palmar Erythema in Persons with Liver Disease and Their Development Following the Administration of Estrogens, Am. J. M. Sc. 204:251, 1942.

2. Bean, W. B.: Acquired Palmar Erythema and Cutaneous Vascular "Spiders," Am. Heart J. 25:463, 1943.

3. Bean, W. B.: A Note on Infrared Photography of Cutaneous Arterial "Spiders" and Hereditary Hemorrhagic Telangiectases, J. Lab. & Clin. Med. 30:190, 1945.

4. Bean, W. B.: The Cutaneous Arterial Spider: A Survey, Medicine 24:243, 1945.

5. Bean, W. B.; Cogswell, R. C.; Dexter, M., and Embrick, J. F.: Vascular Changes of the Skin in Pregnancy: Vascular Spiders and Palmar Erythema, Surg. Gynec. & Obst. 88:739, 1949.

6. Bean, W. B.: A Note on Venous Stars, Tr. A. Am. Physicians 64:100, 1951.

7. Bean, W. B., in discussion on Clinical Pathological Conference, J. Iowa M. Soc. 43:107, 1953.

8. Bean, W. B.: The Natural History and Significance of Certain Vascular Changes in the Skin and Mucous Surfaces (Frederick Robert Zeit Memorial Lecture), Quart. Bull. Northwestern Univ. M. School 27:89, 1953.

9. Bean, W. B.: The Arterial Spider and Similar Lesions of the Skin and Mucous Membrane, Circulation 8:117, 1953.

10. Bean, W. B.: The Caviar Lesion Under the Tongue, Tr. Am. Clin. & Climatol. A. 64:40, 1952.

11. Bean, W. B.: Cherry Angioma: A Digression on the Longevity of Error, Tr. A. Am. Physicians 66:240, 1953.

12. Bean, W. B.: The Changing Incidence of Certain Vascular Lesions of the Skin with Ageing, in Ciba Foundation Colloquia on Ageing: Vol. I. General Aspects, edited by G. E. W. Wolstenholme

and M. P. Cameron, Boston, Little, Brown & Company, 1955, p. 80.

13. Bean, W. B.: Dyschondroplasia and Hemangioma (Maffucci's Syndrome), A. M. A. Arch. Int. Med. 95:767, 1955.

14. Bean, W. B.; Olch, D., and Weinberg, H. B.: The Syndrome of Carcinoid and Acquired Valve Lesions of the Right Side of the Heart, Circulation 12:1, 1955.

Arch. Int. Med. 98:284, 1956.

15. Bean, W. B.: Ophthalmoplegia, Steatorrhea, Phlegectasia, and Vascular Lipomas, A. M. A.

16. Bean, W. B., and Walsh, J. R.: Venous Lakes, A. M. A. Arch. Dermat. 74:459, 1956.

Synthesis and Metabolism of Radioactive Heparin

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Introduction

Heparin synthesis, metabolism, and fate has been an enigma for many years. The following paper is based on the results of a three-year biochemical and clinical study of this fascinating substance. New methods of study were established, including the synthesis and experimental use of radioactive heparin in an effort to elucidate its many problems.

Heparin has been employed clinically for a number of years in the treatment of thrombosis. The rationale for its application is the fact that it is an extremely potent inhibitor of blood coagulation, and consequently it may be expected to be beneficial in thromboembolic diseases. Its effect as an anticoagulant is almost immediate, and it is therefore extremely useful where rapid action is required.[1] Heparin acts primarily on one of the later stages of blood coagulation, i. e., it inhibits the formation of thrombin from prothrombin and, to some extent, prevents thrombin from converting fibrinogen to fibrin. The pharmacological effects of heparin are confined to the blood. It consequently does not interfere with production of prothrombin in the liver (as does bishydroxycoumarin [Dicumarol]); it does not affect blood pressure, body temperature, respiration, or hepatic function. Furthermore, although heparin prolongs clotting time, it does not affect bleeding time, and as a result it can be employed where surgery is involved. On the basis of all the above considerations and a number of others, the present and potential applications of heparin are extremely important and an understanding of its basic biochemistry and physiology is definitely desirable.

In addition to its anticoagulant action, heparin has been found to effect the clearance of lipemic plasma.[2] In this action it appears to take an important part in the transport and metabolism of lipids. There is good evidence that heparin is involved in the activation of a lipoprotein lipase, which effects the metabolic degradation and utilization of ingested fat.[2,3]

From a biochemical point of view, it is also of interest that heparin inhibits certain enzymes.[4] It is also involved in radiation sickness, and it has been claimed to be effective in the treatment of frostbite.[1]

Heparin is a normal constituent of animal organisms, the highest concentration being found in liver and lung. In consideration of this fact, it may be expected that this substance is involved in physiological states, both in normal fat metabolism and in blood fluidity maintenance.

Chemistry

Heparin is a sulfated mucopolysaccharide having a number of structural features in common with hyaluronic acid and chondroitin sulfuric acid. It is a polymer having a molecular weight of about 16,000. The exact chemical structure of heparin is still open to question; however, it is known to be composed of glucosamine, glucuronic acid, and sulfate ester groups. The most probable structure appears to be the repeating tetrasaccharide unit shown in Figure 1.[5]

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The Gilman Laboratory is a part of New York Medical College, Flower and Fifth Avenue Hospitals. Department of Medicine (Dr. Eiber) and Department of Biochemistry (Dr. Danishefsky).

Prepared from a scientific exhibit shown in the Section on Experimental Medicine and Therapeutics at the 106th Annual Meeting of the American Medical Association, New York, June 3-7, 1957.

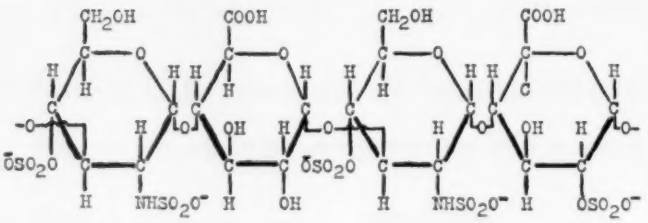

Fig. 1.—Structural formula of heparin. Molecular weight is about 16,000.

Biochemistry and Physiology

The basic biochemistry and physiology of heparin involves a number of problems. Firstly, since heparin is a compound which is a natural component of various tissues, the question arises as to how the body synthesizes it. The heparin content of an organism is not the result of ingested heparin, as is the case with vitamins and some amino acids. On the contrary, the tissues actually synthesize this substance from smaller and less complicated molecules. To know what these precursors are is thus one of the primary requirements for the understanding of heparin metabolism and function.

A corollary to the above problem is the question of the normal turnover rate of heparin. Since the latter is constantly being synthesized and catabolized, the question as to the rate of turnover, the methods of degradation, and the identity of the metabolic products is of considerable significance.

Since heparin normally occurs in living organisms, a second question which has not been answered satisfactorily is what is the physiologic function of this substance. It is known that when heparin is administered to animals it will increase the clotting time of the blood and will also induce the clearing of lipemic blood. In vitro, heparin also has inhibitory effects on certain enzymes; it has some bacteriostatic and a number of other effects. However, it is still an open question as to which, if any, of these activities is the normal function of heparin.

From a purely clinical and pharmacological point of view it is also important to know the mechanism of action of administered heparin, the change it undergoes, the route and rate of excretion, and the form in which it is excreted.

Although all of these can be formulated as separate problems, the information and conclusions in each of these are interdependent. Biochemical studies with heparin are extremely difficult, since very small quantities are involved and the isolation and analytical procedures are either very long or open to criticism. Information on heparin is therefore scanty, and what is known is open to question.

Experimental Studies and Results

In order to solve the problems of biosynthesis use was made in our laboratory of isotopic tracers.

If a specific compound is a precursor of heparin, administration of the former labeled with a radioactive isotope should yield radioactive heparin. The rate of synthesis of the radioactive heparin, or the specific radioactivity of the heparin at different periods after administration of the precursor, would indicate the rate at which heparin is normally synthesized by the body. Applying this approach, it was found that radioactive heparin could be isolated from animals to which radioactive glucose (C^{14}) had been previously administered.[6] This indicated that glucose is involved as a precursor in the biosynthesis of heparin. In a similar manner, administration of radioactive sodium sulfate (S^{35}) resulted in the formation of radioactive heparin containing S^{35}, indicating that sulfate is also a building block for heparin biosynthesis.[7] In other words, the intact living organism

Turnover of Heparin in Various Organs *

Day	Liver	Lung	Spleen
0	100	100	100
1	84.6	89.2	82.3
2	69.0	69.6	69.0
3	56.2	60.1	51.7
4	45.1	48.7	43.1
7	27.2	31.2	28.3
14	4.6	5.2	6.1

* Given as % remaining after a given time.

is capable of synthesizing heparin from glucose and inorganic sulfate.

It might be noted at this point that the radioactive heparin can be extracted from the liver, lung, spleen, or kidney of the animals after injection of the radioactive precursor and that the rate of incorporation or concentration of radioactivity is within the same order of magnitude in all of these organs.

Additional experiments on the rate of this biosynthesis have shown that heparin has a half-life of three and one-half days. In other words, it takes this amount of time for half of the body heparin to turn over and be renewed. Looking at this from another point of view, every three days the living organism catabolizes and synthesizes half of its total heparin. This was found by means of radioactive S^{35} and radioactive heparin. The Table gives the quantitative data on these facts.

In addition to the study of the biosynthesis of heparin, the availability of radioactive heparin allows for the possibility of numerous metabolic studies with this substance which could not have been otherwise carried out.

The first fact which had been definitely established is that heparin is a normal constituent of blood. Previous reports on this question from different laboratories were conflicting, since the purification and assay of minute amounts of heparin was always open to some question. However, the difficulties were overcome by means of radioisotope carrier technique. It was thus shown that heparin is found in normal blood in concentrations of 0.5 mg. per 100 ml.[8]

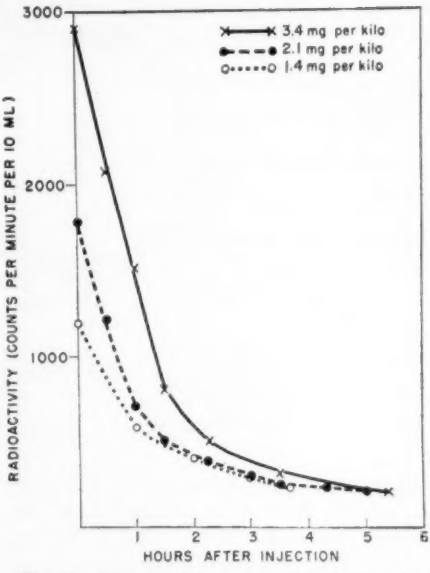

Fig. 2.—Amount of heparin in blood at various time intervals after intravenous injections.

Radioactive heparin has also given a clearer picture as to what happens to this substance when it is injected intravenously.[9]

Thus dogs were given intravenous injections of 1.4, 2.1, 2.8, and 3.4 mg. of radioactive heparin per kilogram. The radioactivity in the blood and its coagulation time were then measured after various intervals. Figure 2 shows graphically the results obtained when 1.4, 2.1, and 3.4 mg. per kilogram were administered. It can be seen that during the first three hours there is a sharp decrease in the amount of radioactivity (or in the heparin concentration) in the blood, after which time it is cleared rather slowly.

The radioactivity measurements indicate that the heparin is cleared from the blood in 5.4 hours when 3.4 mg. per kilogram is administered, in 5 hours when 2.1 mg. is administered, and within 3.7 hours after administration of 1.4 mg. per kilogram. The effect on blood coagulation is extremely pronounced one to two hours subsequent to injection in all cases, after which time it is proportional to the amount of heparin

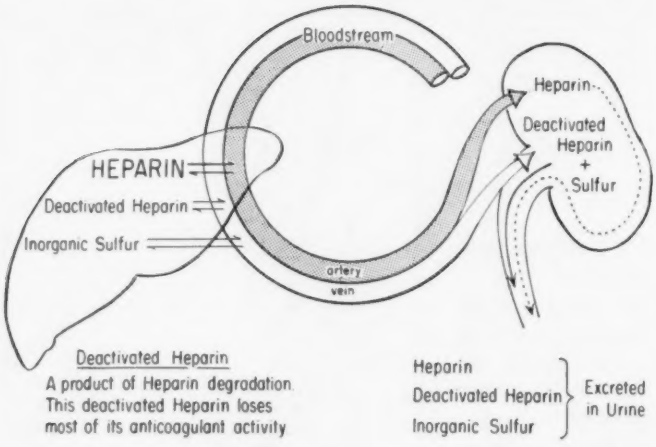

Fig. 3.—"Heparin reserve" concept, showing the route taken after intravenous injection.

(or radioactivity) in the blood. The point of interest in these results is the fact that increasing the dosage from 2.1 to 3.4 mg. per kilogram had a comparatively small effect on the clearance from blood and the duration of pharmacological activity. This would indicate that amounts above a certain critical concentration in the blood are excreted very rapidly, and so the duration of action is not proportional to the amount administered.

This information has definite significance in clinical procedure. It indicates that intravenous dosage of heparin above a certain amount (2 to 2.2 mg. per kilogram) would have comparatively little value as far as the duration of pharmacological effect on blood clotting is concerned. The reason for this is that the blood can hold a specific concentration of heparin for a certain amount of time. Any amount above this concentration is eliminated from the blood very rapidly, and the only time prolongation which would result from higher doses would be the time required for this rapid clearance. As a consequence, the only way to prolong the heparin affect would be to introduce the drug over a long period, as occurs in four-hourly intramuscular injections.

One other question which requires elucidation is where the heparin goes after it leaves the blood stream. Although work on this problem is still being carried out, some preliminary findings can be reported. At a four-hour period after injection, 20% to 25% is found in the liver; about 2%, in the lung, and the rest is distributed in all the tissues. In one case, it was found that some had even found its way into the urine. After 24 hours 25% to 30% of the injected heparin is eliminated in the urine. Elimination of the rest of the drug by this route is very slow and may take over a week. The material which is found in the urine is partially deactivated and desulfated, and there is good indication that this deactivation may take place in the liver (Fig. 3).

The relationship of heparin to lipid metabolism and clearing factor is postulated in Figure 4. It seems remote that a single daily or biweekly injection of heparin could

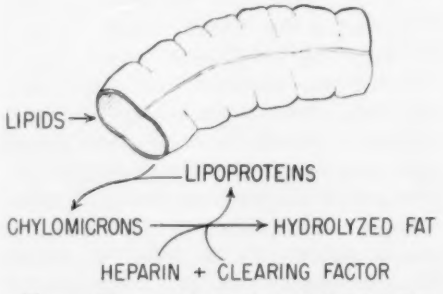

Fig. 4.—The role of heparin in lipid metabolism and its possible association with clearing factor.

have any significant physiologic clinical effect when employed for this purpose. Four-hourly injections appear to be more logical.

Summary

Heparin is a sulfated mucopolysaccharide which is normally present in animal tissues and blood. Its activity as an anticoagulant makes it a compound of basic interest in medicine, and, consequently, a firm understanding of its biochemical and pharmacological action is extremely important. By means of radioactive isotopes it was shown that heparin is synthesized from glucose and inorganic sulfate. The availability of radioactive heparin allows for the study of its metabolism and pharmacological action.

It appears that the optimum dosage for an adult of 150 lb. weight is 50 mg. every four hours when given intravenously.

Larger doses would not proportionately increase the heparin effect and are unwarranted.

The intramuscular route necessitates a slightly higher dosage schedule.

Heparin is a normal constituent of blood in concentrations of 0.5 mg. per 100 ml.

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REFERENCES

1. Jorpes, J. E.: Heparin, London, Oxford University Press, 1946.

2. Hahn, P. F.: Abolishment of Alimentary Lipemia Following Injection of Heparin, Science 98:19-20, 1943.

3. Korn, E. D.: Clearing Factor, a Heparin-Activated Lipoprotein Lipase: II Substrate Specificity and Activation of Cocoanut Oil, J. Biol. Chem. 215:15-26, 1955.

4. Roth, J. S.: Ribonuclease: II. Activators and Inhibitors for Ribonuclease, Arch. Biochem. 44: 265-270, 1953.

5. Wolfron, M. L.; Montgomery, R.; Karabinos, J. V., and Rathgeb, P.: The Structure of Heparin, J. Am. Chem. Soc. 72:5796-5797, 1950.

6. Danishefsky, I., and Eiber, H. B.: Utilization of Glucose in the Biosynthesis of Heparin, Am. Chem. Soc. Abstracts 131:72c, 1957.

7. Eiber, H. B., and Danishefsky, I.: The Incorporation of S^{35}-Sulfate into Heparin, J. Biol. Chem. 226:721-724, 1957.

8. Eiber, H. B., and Danishefsky, I.: Heparin in Blood, Proc. Soc. Exper. Biol. & Med. 94:801-802, 1957.

9. Eiber, H. B., and Danishefsky, I.: Clearance of Injected Herapin from Blood, Nature, to be published.

Encephalopathy in Pulmonary Disease

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It is becoming increasingly clear that cerebrovascular hemodynamics are influenced by alterations in cardiopulmonary physiology. The work of Kety and Schmidt [1] revealed that an increased cerebral blood flow occurs in hypercapnia and in hypoxia. It has also been shown that the increased cerebral blood flow in such situations is followed by increased cerebrospinal fluid pressure.[2] The exact mechanism whereby these changes influence cerebral vascular dynamics is not clear. Clinical syndromes attesting the relationship between cardiopulmonary physiology and cerebrovascular dynamics have been described. Within the past two decades reports have appeared demonstrating signs and symptoms of intracranial disease in patients with primary pulmonary problems. These reports have been well reviewed by Conn et al.,[3] who also added two cases of their own of patients with "emphysematous encephalopathy."

In recent months we have had the opportunity of studying two patients with pulmonary disease associated with clinical findings suggesting the presence of increased intracranial pressure. The primary disease in one patient was pulmonary arteriosclerosis and interstitial pneumonia, and in the second patient it was emphysema and mild congestive heart failure. Presumptive diagnosis on admission of the first patient was brain tumor.

Report of Cases

CASE 1.—A 47-year-old white male office worker was admitted on Jan. 25, 1957, because of recent onset of dizziness, incoordination, and occasional episodes of disorientation. The illness started one week prior to admission, as a "cold," for which he was treated with penicillin by his physician; he apparently became progressively worse until day of admission. No other details of his medical history were available at that time. He was admitted to the hospital with a note from his family physician to the effect that the patient had not been drinking any alcohol prior to admission. This statement was prompted by the ataxic and semistuporous state of the patient when seen by the family physician.

On the night of admission patient was seen by an intern, and he was considered to be fairly comfortable and not critically ill. Only a cursory examination was done at that time. The patient was visited several times during the night by the nurse, and it was presumed that he was sleeping comfortably.

The patient was seen on the following morning and was found to be semicomatose. He appeared quite cyanotic and plethoric and was dyspneic. Blood pressure was 190/100; pulse, 110 per minute. His face was full and showed a ruddy cyanosis. The pupils were bilaterally constricted; visual fields were not determinable. Fundoscopic examination revealed marked engorgement of the retinal veins and moderate papilledema bilaterally. Movement of the tongue was lethargic; speech was thick. Moderate nuchal rigidity was noted. The chest was symmetrical; there were equal excursions bilaterally; bibasilar crepitant rales were heard. The apical rate was 110, and there was a diastolic gallop rhythm clearly heard on auscultation. The left border of dulness was 1 cm. lateral to the midclavicular line. Examination of the abdomen revealed slight distention and no evidence of ascites; the liver edge was palpable 2 cm. below the right costal margin. There was no edema or venous distention in the extremities. Neurological examination revealed generalized areflexia, with no pathological reflexes. Clinical impression was that the comatose state associated with cyanosis, plethora, and history of ataxia and headaches was probably due to an intracranial tumor.

Laboratory work revealed a blood glucose level of 189 mg/100 ml.; blood urea nitrogen, 33 mg/100 ml.; CO_2, 34 mEq. per liter; hemoglobin, 17 gm/100 ml.; hematocrit, 55%; red blood cell morphology revealed polychromatophilia and stippling. Total

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leukocyte count was 13,250 per cubic millimeter, with 51% segmented forms, 2% band forms, 22% lymphocytes, 1% monocytes, and 25% degenerated cells. There were 42 nucleated red cells per 100 leukocytes. Lumbar puncture done at this time revealed an opening pressure of 290 mm. of spinal fluid. Four milliliters of fluid was obtained for laboratory studies, which revealed 10 red cells per cubic millimeter and 1 leukocyte per cubic millimeter. The content of chloride was 117 mEq. per liter and of protein, 8.4 mg/100 ml. (This determination was repeated.) The patient died about 14 hours after admission. The cause of death was considered to be brain tumor.

Autopsy was performed within two hours after death. The positive findings were an interstitial pneumonia in both lungs; pulmonary arteriosclerosis; myocardial hypertrophy and dilatation of the right ventricle; passive congestion of the liver, spleen, and kidneys; marked congestion of the cerebral vessels, and cyanosis of the skin and mucous membranes.

Following the patient's death the wife was consulted regarding his medical history. It was revealed that the patient was in good health up to two years prior to admission. In April, 1955, he was hospitalized for eight days because of pneumonia. The hospital records revealed that he had an extensive pneumonic infiltration of the entire right lower lung. He was treated with penicillin, 600,000 units per eight hours, and responded by becoming afebrile in two days. At that time patient was noted to be quite lethargic. He also had "thick speech" and a vacant stare and was confused. Laboratory work at that time revealed a hemoglobin value of 14.8 gm/100 ml.; hematocrit, 48%; normal erythrocyte morphology. Total leukocytes were 10,100 per cubic millimeter with 28% segmented forms, 44% band forms, 1% metamyelocytes, 17% lymphocytes, and 10% monocytes. Urine showed 1+ glycosuria. (Blood sugar on the following day was 87 mg/100 ml.) Electrocardiogram was interpreted as within normal limits. Because of a diagnosis of meningitis entertained at that time, a lumbar puncture was performed. Opening pressure was 250 mm.; cell count revealed 1 lymphocyte per cubic millimeter; total protein, 8.4 mg/100 ml. (*sic*), chlorides (as NaCl), 690 mg/100 ml.; glucose, 129 mg/100 ml.; Kahn and colloidal gold, negative. He was treated symptomatically and was discharged after eight days of hospitalization, at which time the process in his right lung had cleared.

The patient did fairly well until October, 1956, four months prior to the final admission. He had complained of not feeling too well at that time. He had several episodes of upper respiratory infections between October, 1956, and January, 1957, for which he was treated with penicillin, without sustained clinical improvement. His wife reported that during the month of January, 1957, during the three-week period just prior to admission, the patient became stuporous and had memory lapses on several occasions. He was also noted to have a ruddy cyanotic appearance at that time. Because of his stuporous and ataxic episodes it was thought that the patient had been consuming alcohol, but this was denied by the wife and by the patient. He kept "staggering around" with thick speech until the time of his final admission to the hospital.

Comment.—The autopsy findings revealed an interstitial pneumonia superimposed on pulmonary arteriosclerosis, with right ventricular enlargement and failure. It is likely that the encephalopathy during the previous admission is similar to the one on the final admission. No evidence of brain tumor was found. The right-sided failure in this patient was secondary to pulmonary disease.

CASE 2.—A 57-year-old white woman was admitted from the emergency room because of severe dyspnea, swelling of both feet and ankles, and moderate right upper quadrant abdominal pain. These symptoms had been progressive for three to four weeks prior to admission. She had not seen her family physician for the preceding six weeks. She reported that she was known to have chronic congestive heart failure and chronic emphysema and had been maintained with digitalis, diuretics, low-salt diet, expectorants, bronchodilators, and mucolytic agents. Apparently she had had no recent response to acetazolamide (Diamox). Past medical history was mainly confined to the long-duration illness described above. Review of systems revealed that patient suffered from severe headaches and had several spells of disorientation, semistupor, and blurred vision.

Physical examination on admission revealed a well-developed obese white woman in obvious dyspnea and with moderate cyanosis of the lips. Temperature, 98.8 F; blood pressure, 130/85; pulse, 96 and regular; no nuchal rigidity; no retinopathy; lungs revealed decreased breath sounds over upper lung fields and crackling rales over lower lung fields bilaterally. There was no evidence of consolidation. Heart sounds were distant; no murmurs were heard. Left border of dulness was 1.5 cm. lateral to midclavicular line. The abdomen was obese and appeared distended; no fluid wave was elicited; liver was smooth and was enlarged to 4 cm. below the right costal margin. The lower extremities were obese and swollen, with 4+ pitting edema from the feet to lower half of the thighs. Pedal pulses were not palpable; femoral and popliteal pulses were intact. Neuro-

logical examination was within normal limits. Clinical impressions at this time were congestive heart failure (with hypervolemia) secondary to chronic lung disease and to arteriosclerotic heart disease.

Chest x-ray on admission revealed a slight prominence of vascular markings, mainly confined to the left side. These findings were regarded as being consistent with pulmonary congestion and an accompanying inflammatory infiltration in the left lung base. Bilateral bibasilar calcifications were present. The cardiac silhouette revealed an accentuation of the left ventricle. Electrocardiogram revealed semivertical position with the QRS vector directed posteriorly. The QRST angle was normal. No evidence of right strain.

Laboratory work revealed hemoglobin value of 16.3 gm/100 ml.; hematocrit, 52%; total leukocytes, 6000, with 68% segmented neutrophils, 20% lymphocytes, and 2% monocytes. Serum Na was 137 mEq. per liter; K, 4.8 mEq.; Cl, 109 mEq., and CO_2, 31 mEq. Serum proteins were normal. Urinalysis was essentially normal.

Patient was treated with mercaptomerin (Thiomerin) and aminophylline intravenously; was continued on a low salt diet, isoproterenol (Isuprel) four times daily, oxygen mask, and digitalis, 0.1 gm. daily. In the first 36 hours following admission patient excreted 4900 cc. by diuresis. The peripheral edema improved considerably; the lung findings had improved, but there were bibasilar crackling rales. She continued to improve during the next five days except for occasional burning epigastric pain, for which the patient, of her own volition, took Tums (calcium carbonate precipitate, magnesia carbonate, magnesia trisilicate, oil of peppermint, and sugar), with relief. Occasional episodes of shortness of breath were relieved by isoproterenol by nebulizer. On the sixth hospital day the patient was observed to become quite restless and cyanotic. She lapsed into a semicomatose state during the night. She was treated symptomatically, was placed under an oxygen tent for three hours, and was improved. Serum electrolytes next morning were as follows: Na, 139 mEq. per liter; K, 5.0 mEq.; Cl, 96 mEq.; CO_2, 33 mEq., and blood urea nitrogen, 10 mg/100 ml. Symptomatic improvement from congestive heart failure continued; the peripheral edema receded, and no pulmonary rales were heard. Occasional episodes of dyspnea were controlled by the use of isoproterenol, liquids, and expectorants. Serum electrolytes on the eighth (May 13, 1957) hospital day revealed Na, 141 mEq. per liter; K, 5.4 mEq.; Cl, 91 mEq., and CO_2, 39 mEq. On the following day these levels were essentially the same except for a decrease of the CO_2 to 34 mEq. per liter. The patient was treated with acetazolamide for the next five days. She did very well symptomatically. Electrolytes four days later revealed (May 22, 1957) Na, 143 mEq. per liter; K, 5.5 mEq.; Cl, 102 mEq.; CO_2, 28 mEq. On May 23, eighteen days after admission, patient was being prepared for discharge. On that morning patient was noted to be quite drowsy and somnolent. Physical examination revealed blood pressure, 150/100; pulse 92 per minute, and respirations 40 per minute. There was moderate nuchal rigidity; pupils were bilaterally constricted. Funduscopic examination revealed markedly engorged retinal veins and marked papilledema bilaterally; lungs, decreased breath sounds and minimal amount of bibasilar crackling rales. Heart, apex rate 92; no murmurs. Abdomen, no distention, soft; liver, barely palpable. Neurological findings, complete areflexia, no muscle strength; muscle strength, considerably decreased; no pathological reflexes. Patient was confused and somewhat disoriented.

Lumbar puncture at this time revealed the opening pressure of 500 mm. of cerebrospinal fluid. Three milliliters was removed for laboratory studies, which revealed 1 leukocyte and 1 red cell per cubic millimeter; proteins, 15 mg/100 ml.; chloride, 112 mEq. per liter; colloidal gold curve and Kahn test, negative. Serum CO_2 at this time was 35 mEq. per liter. The patient was treated symptomatically with intravenous fluids (10% dextrose in water) and improved within 10 hours. The patient continued to improve and was discharged after 25 days in the hospital. Serum electrolytes on the day prior to discharge were as follows: Na, 132 mEq. per liter; K, 5.4 mEq.; Cl, 103 mEq., and CO_2, 35 mEq. She was discharged with a regimen of low-salt diet, digitalis, expectorants, and isoproterenol by nebulizer, to the care of her family physician.

Comment.—This patient had a history of chronic cardiopulmonary disease. Previous episodes of the encephalopathy were described by the patient. The present episode occurred after the patient had responded fairly satisfactorily to treatment for congestive heart failure.

Comment

Both patients described here presented symptoms and signs of increased intracranial pressure during their hospitalization. The clinical diagnosis of brain tumor was made on Case 1 prior to his death. Case 2 developed the signs and symptoms of increased intracranial pressure during her hospital stay. The history of both patients revealed

episodes of disorientation, confusion, ataxia, severe headaches, and "thick speech." Both patients showed evidence of secondary polycythemia and the ruddy cyanosis associated with the polycythemia.

Postmortem examination of Case 1 revealed no evidence of primary brain disease. The smoothing of the cerebral surface was associated with elevated cerebrospinal fluid pressure. In Case 2 the signs of increased intracranial pressure disappeared on symptomatic therapy. The marked papilledema and retinal vein engorgement observed during her episode of encephalopathy were associated with a markedly elevated cerebrospinal fluid pressure. Lumbar puncture was not repeated, but the findings of venous engorgement as well as papilledema had disappeared within 10 hours, at which time the patient was symptomatically better.

The mechanism of this syndrome of encephalopathy associated with pulmonary disease has been suggested as being due to the hypercapnia and hypoxia, secondary to the decreased ventilation in the lungs, whether secondary to an infectious process, to pulmonary edema, or to vascular problems. The hypercapnia and hypoxia are presumed to cause cerebrovascular dilatation, with subsequent edema and congestion of the brain.[4] It is interesting, in this connection, to note that although these two patients had evidence of pulmonary disease and high levels of CO_2 (chemical determination) the episode of encephalopathy in Case 2 did not coincide with the highest levels of CO_2. It might be suggested that other biochemical changes associated with the hypercapnia might mediate the marked cerebrovascular dilatation of this syndrome. Unfortunately, blood pH determinations were not done in these patients. It is suggested that the biochemical changes related to chronic cardiopulmonary disease apparently provide the basic electrolyte alterations upon which acute infectious processes, or acute exacerbations of respiratory insufficiency, impose additional alterations to precipitate the syndrome. In one previous case reported, pulmonary arteriosclerosis was considered as contributory.[5] Case 1 in this paper also had evidence of pulmonary arteriosclerosis.

The spinal fluid protein levels have been observed to be low in patients with this syndrome. This is true in the patients reported here and also in the patients of Conn et al.[3] The mechanism of this change is not clear. It might be suggested that the mechanism might involve an alteration in the permeability of the dilated vessels, permitting the diffusion of perivascular fluid into the cerebrospinal fluid system. It has been suggested by Beaumont and Hearn that there might be an alteration in the filtration processes of the arachnoid villi.

The syndrome described here is undoubtedly of more widespread occurrence than is evident from the literature. Although the reports of papilledema in pulmonary disease date back to 1882,[6] the number of reports is relatively scanty. It is important to establish the diagnosis in such cases and to differentiate this syndrome from brain tumor, cerebrovascular accidents, hypoglycemia, and thromboembolic problems. The outstanding features of this syndrome of the encephalopathy due to decreased respiratory exchange are (*a*) underlying lung disease, whether primarily ventilatory or diffusion defects, (*b*) evidence of secondary polycythemia, (*c*) clinical pattern of headaches, stupor, or coma, associated with areflexia or with focal neurological signs, (*d*) increased cerebrospinal fluid pressure associated with papilledema and retinal vein engorgement, and (*e*) low cerebrospinal fluid proteins.

Summary

Two cases are presented with symptoms and signs of increased intracranial pressure due to primary problems related to pulmonary exchange. The outstanding features of this syndrome appear to be (*a*) underlying ventilatory or diffusion defects in the lungs, (*b*) clinical pattern of headaches, stupor, or coma associated with areflexia or with focal neurological signs, (*d*) increased cerebrospinal fluid pressure associated with

papilledema and retinal vein engorgement, and (*e*) low cerebrospinal fluid proteins. The possible mechanisms are discussed.

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REFERENCES

1. Kety, S., and Schmidt, C. F.: Effect of Altered Tension of CO_2 and O_2 on Cerebral Blood Flow and Cerebral O_2 Consumption in Normal Young Men, J. Clin. Invest. 27:484-492, 1948.

2. Ryder, H. W., et al.: Influence of Changes in Cerebral Blood Flow on Cerebrospinal Fluid Pressure, A. M. A. Arch. Neurol. & Psychiat. 68: 165-169, 1952.

3. Conn, H. D.; Dunn, J. P.; Newman, H. A., and Belkin, G. A.: Pulmonary Emphysema Simulating Brain Tumor, Am. J. Med. 22:524-533, 1957.

4. Simpson, T.: Acute Respiratory Infection in Emphysema: An Account of 118 Cases, Brit. M. J. 1:297-301, 1954.

5. Meadows, S. P.: Papilledema Associated with Chronic Bronchitis, Emphysema and Polycythemia, Proc. Roy. Soc. Med. 40:555, 1947.

6. Mackenzie, S.: Med. Times & Gaz. 2:765, 1882; cited by Cameron, A. J.: Marked Papilloedema in Pulmonary Emphysema, Brit. J. Ophth. 17:167, 1933.

Parathyroid Crisis

A Cause of Sudden Death

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Sudden death from hyperparathyroidism is not common. It can be prevented. Just as thyroid storm is a fulminating increase in the manifestations of hyperthyroidism, the majority of instances of parathyroid crisis occur as acute exacerbations of chronic hyperparathyroidism. Two major factors have been suggested which precipitate a crisis: high calcium intake, as in an ulcer regimen where antacids containing absorbable calcium are used, and immobilization, which increases the rate of skeletal demineralization.[1] The end-result is an abnormal increase in serum and urinary calcium and phosphorus, followed by a rapid death. The mechanism of death presumably is cardiac poisoning by calcium with cardiac arrest in systole.

This disease is often misdiagnosed or overlooked completely, yet it can be diagnosed rather easily and a cure almost assured. A thorough understanding of parathyroid crisis is necessary, therefore, if this disease is to be recognized and treated in time.

Report of a Case

A 38-year-old man, who had been in the trucking business for eight years, had noted the onset of nausea, vomiting, and constipation plus a 17 lb. weight loss over a four-week period. The patient stated he had been eating baby food with some relief for the three days prior to admission. He was sent to the hospital as an outpatient for an upper gastrointestinal series. In the radiology department, he felt so faint and extremely weak that the usual roentgenograms could not be taken. It was thought that the patient should remain in the hospital for further observation.

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He had had shortness of breath since childhood and claimed he had been rejected by the army because of a heart murmur and ankle edema. He had noted the onset of progressive easy fatigue five years prior to admission. He had been subject to severe intermittent lower abdominal pains resembling renal colic for two to three years but had not noted passage of urinary stones. The patient's wife claimed he had occasional hematuria and noted, in the last year, that he choked and could not get his breath when lying on his back. In the six months prior to admission, the patient consumed at least 2-3 qt. of milk daily because of a stated desire for "something cold."

Physical examination revealed a blood pressure of 90/66; pulse, 104 and regular, and respirations 28 per minute. The patient appeared well nourished and well developed but looked extremely apprehensive. A 1 cm. nodule was palpated in the region of the right lower lobe of the thyroid gland. The heart appeared to be within normal limits. There were coarse inspiratory and expiratory rhonchi in the lungs, which cleared somewhat on coughing. Findings on neurologic examination were normal. Admission hemoglobin was 14 gm. %; WBC, 21,600 per cubic millimeter, with a differential of 86% polymorphonuclear cells, 8% stab forms, 5% lymphocytes, and 1% monocytes. Hematocrit was 44%. Urine examination showed specific gravity of 1.010, acid reaction, and 3+ protein. The urine was loaded with WBC and a few amorphous crystals.

Fig. 1.—Bisected parathyroid adenoma in substance of thyroid gland and paratracheal tissue.

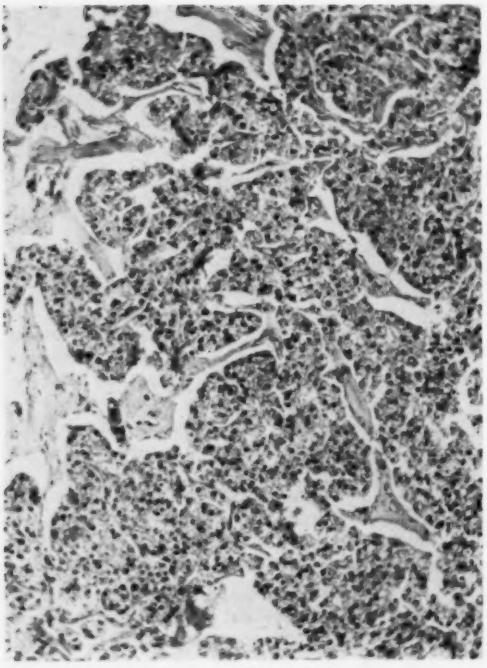

Fig. 2.—Low-power photomicrograph of parathyroid adenoma, showing chief cells and variation to the water-clear cell type; ×100.

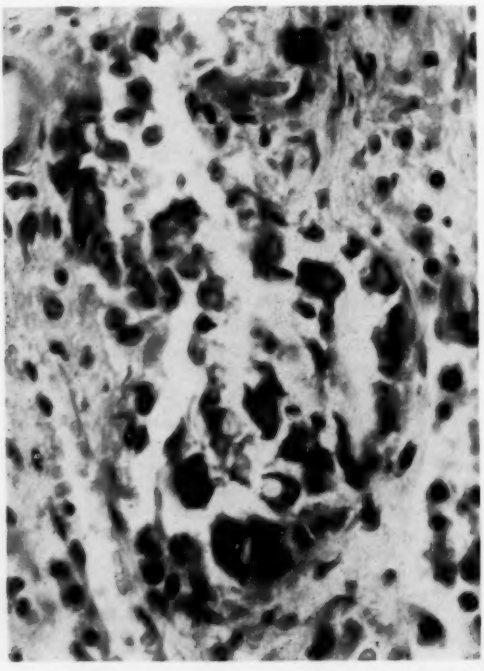

Fig. 3.—High-power photomicrograph, showing calcium deposits in kidney tubule; ×430.

Summary of Major Clinical Features with Frequency of Occurrence in Twenty-Three Reported Cases of Parathyroid Crisis

Clinical Features	Cases, No.
Anorexia, nausea, vomiting	21
Asthenia	21
Abdominal pain	15
Bone pain	14
Weight loss	13
Fever	11
Cervical mass	8
Constipation	7
Ulcer history	6

In the afternoon of admission some basilar rales were noted bilaterally and the patient appeared slightly cyanotic. His weakness prevented him from walking. Later, while a consulting physician was talking to him, the patient suddenly stopped breathing and became pulseless. Cardiac massage and intracardiac epinephrine were able to effect only transient impulses. The patient was declared dead nine and one-half hours after admission.

At autopsy, a large spherical well-encapsulated mass, measuring 5 cm. in diameter, was noted to be confluent with the right lower parathyroid gland (Fig. 1). On microscopic examination of this mass, the typical histological pattern of a parathyroid adenoma was found, involving proliferation of chief cells with variations to the water-clear cell type (Fig. 2). There was also some evidence of old hemorrhage. There were multiple areas of calcium deposition and secondary inflammation in the kidneys (Fig. 3). Bone sections contained many areas of osteoclastic bone resorption, with fibrosis around trabeculae. An early confluent pneumonia was present and a moderately congested liver, but there was no evidence of ulceration anywhere in the gastrointestinal tract.

Laboratory studies subsequently performed on a blood sample obtained at the time of admission were as follows: serum calcium, 18.9 mg. %; phosphorus, 5.2 mg. %; sodium, 135 mEq. per liter; total proteins, 5.6 gm. %; albumin, 2.9 gm. %; globulin, 2.7 gm. %; alkaline phosphatase, 4.5 Bodansky units. The Sulkowitch test was positive for calcium.

Comment

The case presented is typical of the 22 previously reported instances of parathyroid crisis.[1-6] In virtually all of the reported cases, an acute episode was superimposed on chronic hyperparathyroidism, evidenced by kidney stones or metastatic calcium deposits and bone changes (Table). It is thought that kidney stones or calcium deposition may precede bone changes by several years.[7] In fact, Albright states that the degree of bone changes is an index of duration of disease rather than of severity.[8] Since in the present case in addition to the long history there were renal calcifications and early osteitis fibrosa, one may assume this patient, also, had chronic hyperparathyroidism.

Eight-six per cent of the cases of hyperparathyroidism are due to functional adenomas.[9] All but 3 of the 23 reported cases of parathyroid crisis were due to parathyroid adenomas. Of these three cases, one was caused by overdosage with parathyroid extract[10]; another was due to a parathyroid carcinoma,[4] and the third was reported as frank hyperplasia.[11] Virtually all cases of parathyroid crisis, therefore, are due to adenomata, and these usually are solitary.

The acuteness of onset of symptoms is the one distinguishing clinical feature between parathyroid crisis and ordinary chronic hyperparathyroidism. The diagnosis, therefore, must evolve from the same diagnostic criteria as apply to hyperparathyroidism in general. Vagueness of symptoms is characteristic of hyperparathyroid disease and often results in many overlooked or misdiagnosed cases. Hurxthal and Musulin[9] list the usual symptoms under four categories:

1. General systemic complaints of fatigue, weakness, aching muscles, headache.

2. Gastrointestinal symptoms consisting of polydipsia, mild abdominal discomfort, duodenal ulcer distress, dry throat, anorexia (distaste for milk and eggs often).

3. Genitourinary symptomatology—polyuria, renal colic, dysuria, nocturia, eneuresis, hematuria, pyuria.

4. Disorders referable to the osseous system, including peripheral bone pain, backache, fractures, bone cysts, shrinking stature, pigeon breast, and tumors of jaw, metacarpals, vertebrae, long bones.

As in this case, it is not uncommon to be mislead by the coexistence of peptic ulcer and hyperparathyroidism. If the ulcer is

treated with standard diets and antacids, the calcium intake is bound to increase, which may lead to parathyroid crisis. Six of the cases recorded in the literature had an ulcer history and were treated accordingly.[1,2,6] The patient in the present case had symptoms very suggestive of peptic ulcer and had an abnormally high intake of calcium rich foods, which undoubtedly played a major role in the development of parathyroid crisis.

Pain is an almost constant feature of impending crisis. Fifteen of the twenty-three cases had abdominal pain in varying degrees.[1-3,6] This ranged from mild discomfort to the severe incapacitating type, resembling renal colic or other acute abdominal disease. Chest pain and aches misinterpreted as cardiac, rheumatic, or arthritic in origin are fairly common. In 14 of the recorded cases, bone pains were noted.[1,2,4-6] Some of these pains were related to fractures; some, to severe backache, and others, to exquisitely tender areas, usually in long bones.

Asthenia has been recorded in all but two of the patients[1-6] and can be assumed to accompany parathyroid crisis. The degree of weakness and lassitude is far severer than one would expect to see in psychoneurosis or the general malaise of less severe diseases.

Equally constant are the anorexia, nausea, and vomiting, which are manifestations of this disease. It is often these symptoms and severe weight loss, recorded in 13 of the 23 cases,[1-6] which cause the patient to seek a physician.

The presence of a cervical mass often mistaken for a thyroid nodule was noted in one-third of the patients with parathyroid crisis.[1,2,4] Tracheal compression by the adenoma was probably responsible for the "choking sensation" noted in the present case and is reported to have caused episodes of coughing and sneezing on dorsiflexion of the neck in another case.[12]

Some additional clinical features may help identify this disease. Often, there is a disproportionately high pulse rate in spite of increasing drowsiness. This plus high fevers of unknown etiology are recorded in over 50% of the cases. Constipation was observed in one-third of the cases. "Band keratitis," which Cogan[13] describes as calcification in the superficial layers of the cornea, may be present. Also, calcium deposits in the conjunctivae and palpebral fissures are occasionally seen. Mental aberrations and even psychoses are fairly common findings and often mask the underlying disease.[2,5,6]

Undoubtedly, the next most important diagnostic feature, after the physician's high index of suspicion and diagnostic agility, is elevation of the serum calcium. A serum calcium of 17 mg. %, according to Albright,[8] is the critical level above which the symptoms of parathyroid crisis may be expected to ensue. At these exceptionally high levels of serum calcium, the serum inorganic phosphorus also tends to rise because it can no longer be excreted by the kidneys.[8] This is an extremely grave prognostic sign, and immediate measures should be taken to reduce the serum calcium. Albright describes the danger signals of parathyroid crisis as rising serum calcium, phosphorous and NPN levels and a sharp fall in urine volume.[8] Since an elevated urine calcium accompanies hypercalcemia, a good easy preliminary examination is the Sulkowitch test, which is always positive in hypercalcinuria.[14] If the patient is in parathyroid crisis, the serum analysis will enable the physician to make a definite diagnosis.

Roentgenologic examination often is a useful adjunct in diagnosis. Demonstrations of renal or other organ calcifications and the presence of a diffuse shadow in the neck or mediastinum should suggest the possibility of hyperparathyroid disease. Pathologic fractures, bone cysts, or evidence of bone decalcification may add further support to the diagnosis.

Surgical extirpation is the treatment of choice at the present time. Six of twenty-three cases were completely relieved when the parathyroid adenoma was removed.[1,4-6]

Unfortunately, one of these had parathyroid carcinoma and succumbed later to recurrent tumor.[4] One other died subsequently of hypertension and renal insufficiency,[15] which is the common cause of late mortality after surgery in parathyroid disease. In such cases, renal damage is often too far advanced when the disease is recognized to effect more than temporary relief of symptoms. As most of the patients in parathyroid crisis are dehydrated, James and Richards [1] suggest hydration with isotonic saline before surgery to minimize hypochloremia. They also recommend that pressor agents be given to prevent shock preoperatively. The use of chelating agents may prove effective by a transient lowering of the serum calcium to maintain the patient during the emergency period until surgery can be performed with safety. Agents such as edathamil are under experimental study, but severe internal hemorrhages and renal tubular necrosis have hampered their extensive use to date.[16]

Summary

The acute phase of hyperparathyroidism, parathyroid crisis, is uncommon and easily misdiagnosed and may prove rapidly fatal. This condition is characterized by an acute exacerbation of the signs and symptoms of chronic hyperparathyroidism, with a precipitous rise in serum calcium and eventually in phosphorus levels. The critical level of serum calcium seems to be 17 mg. %. A high calcium intake and/or immobilization may precipitate crisis in a patient with hyperparathyroidism. The 23d case of parathyroid crisis is presented, the diagnosis having been established at autopsy. The clinical picture of this disease is reviewed and discussed. Surgical intervention offers the best chance of survival at present, although the use of chelating agents for temporarily lowering serum calcium may prove an effective means of treatment in the future.

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REFERENCES

1. James, P. R., and Richards, P. G.: Parathyroid Crisis: Treatment by Emergency Parathyroidectomy, A. M. A. Arch. Surg. 72:553-566 (April) 1956.

2. Mellgren, J.: Acute Fatal Hyperparathyroidism, Acta path. et microbiol. scandinav. 20:693, 1943.

3. Alexander, H. B.; Pemberton, J. de J.; Kepler, E. J., and Broders, A. C.: Functional Parathyroid Tumors and Hyperparathyroidism, Am. J. Surg. 65:157-188 (Aug.) 1944.

4. Young, J. H., and Emerson, K., Jr.: Parathyroid Carcinoma Associated with Parathyroid Intoxication, Ann. Int. Med. 30:823-837 (April) 1949.

5. Goldman, L.: Unusual Manifestations of Hyperparathyroidism, Surg. Gynec. & Obst. 100: 675-689 (June) 1955.

6. Bradlow, B. A., and Segal, N.: Acute Hyperparathyroidism with EKG Changes, Brit. M. J. 2:197-200 (July 28) 1956.

7. Chute, R.: Clinical Aspects of Hyperparathyroidism with Special Reference to Urology, J. Urol. 41:762-772 (May) 1939.

8. Albright, F., and Reifenstein, E. C., Jr.: Parathyroid Glands and Metabolic Bone Disease, Baltimore, Williams and Wilkins Company, 1948.

9. Hurxthal, L. M., and Musulin, N.: Clinical Endocrinology, Philadelphia, J. B. Lippincott Company, 1953.

10. Lowenburg, H., and Ginsburg, T. M.: Acute Hypercalcemia: Report of a Case, J. A. M. A. 99:1166 (Oct. 1) 1932.

11. McClure, R. D., and Lam, R. T.: End Results in the Treatment of Hyperparathyroidism, Ann. Surg. 121:454-469 (April) 1945.

12. Foster, A. H., Jr., and Nichol, W. W.: Parathyroid Adenoma: A Case Report with Unusual Clinical Features, Ann. Surg. 145:279-281 (Feb.) 1957.

13. Cogan, D. E.: Unpublished data, quoted by Albright and Reifenstein (1948).

14. Baird, I. M.; Grainger, R., and Rowlands, B. C.: Hyperparathyroidism Due to Parathyroid Adenoma: Report of 6 Cases and a Review, Brit. J. Surg. 42:140-151 (Sept.) 1954.

15. Waife, S. O.: Parathyrotoxicosis: Syndrome of Acute Hyperparathyroidism, Am. J. M. Sc. 218:624-635 (Dec.) 1949.

16. Dudley, H. R.; Ritchie, A. C.; Schilling, A., and Baker, W. H.: Pathologic Changes Associated with the Use of Sodium Ethylene Diamine Tetra-Acetate in the Treatment of Hypercalcemia: Report of 2 Cases with Autopsy Findings, New England J. Med. 252:331-337 (March 3) 1955.

Case Reports

Meningitis Due to Mima Polymorpha

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Although meningococcal meningitis is not usually difficult to diagnose, a similar clinical and pathological picture may sometimes be produced by organisms other than Neisseria meningitidis.[4] This point was demonstrated to us recently by a patient with meningitis due to Mima polymorpha.

M. polymorpha is a species of the tribe Mimeae, which was named by De Bord,[1] in 1939, because this unusual group of Gram-negative bacilli closely mimicked neisseriae. Later, De Bord noted the presence of M. polymorpha in both normal and inflamed vaginae.[2,3] In 1945, Deacon[5] recovered this bacillus from war wounds, a chancroid lesion, brain tissue after head injury, and cases of resistant gonorrhea in the male. Thereafter, De Bord,[6] and subsequently Townsend et al.[7] described patients with M. polymorpha meningitis. A closely related organism was cultured from the meninges at autopsy in Schuldberg's case.[4] Subacute bacterial endocarditis,[8] septicemia,[9] and urinary tract infections[10] have also been caused by this bacterium.

The primary purpose of the following case report is to emphasize the striking clinical similarities between M. polymorpha meningitis and meningococcal meningitis.

Report of Case

A 19-year-old airman was admitted to the hospital in a semicomatose condition on April 19, 1957.

He had been well until the morning of the day of admission, when he complained to friends of a severe headache. Later that day he began to stagger and vomit, and that night he became delirious and was brought to the hospital.

On examination in the emergency room, the patient had a rectal temperature of 98 F, a pulse of 104, a respiratory rate of 18, and a blood pressure of 105/70. The patient vomited intermittently and was incontinent of urine and feces. The fists and jaws were tightly clinched; the extremities exhibited violent purposeless movements, and the eyes rolled wildly. He did not respond to the spoken voice, but he did react strongly to painful stimuli. The pupils were equal and reacted to light; the neck was supple, and the deep tendon reflexes were symmetrically hyperactive. No other abnormalities were noted at this time.

About an hour later the rectal temperature had risen to 104 F; the pulse was 138, and the blood pressure was 136/70. Many reddish petechiae 0.2 to 1 cm. in diameter were visible over the trunk and extremities. There was definite stiffness of the neck. A lumbar puncture revealed grossly cloudy cerebrospinal fluid; pressure readings were not attempted.

Laboratory Data.—On admission, the white blood cell count was 36,000 per cubic millimeter, with 82% neutrophils, 7% juveniles, 10% lymphocytes, and 1% monocytes. The total eosinophil count was zero. The volume of packed red cells was 47%. The urinalysis was normal except for 2+ sugar. The blood glucose (Folin-Wu) was 270 mg. per 100 ml. Two blood cultures revealed no growth. No cultures of the skin lesions were made. However, Gram-stained smears of the scrapings taken from several abdominal petechiae showed no bacteria. On the fourth hospital day the white blood cell count, differential count, blood sugar value, and urinalysis were normal. The cerebrospinal fluid findings are recorded in the Table.

Course.—The initial clinical impression was meningococcal meningitis. Therefore, during the first two days of therapy the patient received a total of 48,000,000 units of penicillin intravenously.[12] In addition, 200 mg. of hydrocortisone was administered intravenously, even though no evidence for adrenal insufficiency ever developed.

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Cerebrospinal Fluid Studies *

	April 19	April 25	May 7	May 14	May 27
Cells/cu. mm.	2,280	130	36	35	12
Neutrophils, %	97	20	—	—	2
Lymphocytes, %	3	110	—	—	10
Open press., mm. water	—	240	220	205	150
Clos. press., mm. water	—	210	180	160	120
Protein, mg./100 ml.	280	69	28	30	84
Sugar, mg./100 ml.	23	—	—	72	42
Culture	Pos.	Neg.	Neg.	Neg.	Neg.

* — signifies no determination attempted.

After 24 hours of treatment the patient was less disturbed and the rectal temperature had fallen to 101 F. By the third hospital day, the cutaneous petechiae had largely disappeared and the patient was afebrile. The intravenous medication was stopped at this point, and for the next five days the treatment consisted of 1,000,000 units of aqueous penicillin given intramuscularly every three hours.

One week after admission the patient was clinically well. However, 600,000 units of procaine penicillin was injected intramuscularly every six hours until the 11th hospital day, when all specific therapy was discontinued.

Thereafter the patient's course was uneventful, and he was discharged to full duty on the 35th hospital day.

Bacteriology.—A direct smear of the patient's spinal fluid revealed numerous intracellular Gram-negative diplococci which resembled Neisseria gonorrhoeae more than Neisseria meningitidis. Extracellular Gram-negative diplococci, as well as a few Gram-negative bipolar coccobacilli, were seen. It was noted that several of these micro-organisms retained portions of the primary dye. The degree of pleomorphism exhibited on microscopy was suggestive of either a species of Neisseria, an organism similar to Neisseria, or the presence of two micro-organisms.

Bacteriological studies confirmed the pleomorphic activity of this organism, since bacillary forms were predominant in broths, while diplococcal forms were predominant on agars. Biochemical and carbohydrate fermentation studies were negative, and the catalase reaction was positive. The indophenol oxidase enzyme, a true Neisseria characteristic, was not produced. Consequently, this organism was identified as M. polymorpha. (Occasionally certain strains of this bacterium give a positive oxidase reaction and are designated M. polymorpha var. oxidans).

Disk sensitivity studies showed this strain of M. polymorpha to be sensitive to erythromycin, penicillin, dihydrostreptomycin, novobiocin (Cathomycin), chloramphenicol, oxytetracycline, and chlortetracycline.

"Bergey's Manual of Determinative Bacteriology" [16] classifies this organism as belonging to the tribe Mimeae, which includes three genera: Mima, Herellea, and Colloides. Several excellent review articles describe in detail the differentiation of these genera by routine bacteriological procedures.[2,7,12] A more rapid means of differentiating this organism from Neisseria is the recently described precipitin technique.[10]

Comment

This is the fifth reported case of meningitis due to M. polymorpha.[4,6,7] In each instance the clinical picture was indistinguishable from and initially considered to be meningococcal menigitis. This confusion in diagnosis developed because four of the patients had a generalized petechial rash,[4,7] and all five of them had Gram-negative diplococci in either the cerebrospinal fluid,[6,7] blood,[7] or skin lesions.[4,7]

In contrast to the other articles on M. polymorpha meningitis, this report is the first in which the details of therapy are described. Similarly, our patient is the first to be cured by penicillin. De Bord's case responded well to the sulfonamides,[6] whereas a combination of these agents was effective in another patient.[7] Several in vitro studies have shown that M. polymorpha is sensitive to a large number of antibiotics.[7,8,11,12] In this respect it is noteworthy that Pike's patient with subacute bacterial endocarditis recovered following the use of oxytetracycline.[8]

Two deaths have resulted from this form of meningitis. One patient died before adequate therapy was instituted.[7] The other died seven hours after admission to the hospital, despite treatment with penicillin and the sulfonamides.[4] Examination at autopsy in these cases revealed generalized petechiae throughout the skin and viscera, together with acute leptomeningitis and gross hemorrhage in the adrenal glands.

Summary

A case of meningitis due to Mima polymorpha is described, and its striking clinical similarity to meningococcal meningitis is emphasized.

M. polymorpha is a Gram-negative organism which closely resembles Neisseria. Identification is based upon its pleomorphic activity in different media, negative biochemical and carbohydrate fermentation studies, a tendency to retain portions of the primary dye, and a positive catalase reaction. The oxidase reaction is variable.

In both meningococcal and M. polymorpha meningitis, a generalized petechial rash is commonly present, and Gram-negative diplococci are characteristically found in the skin lesions, cerebrospinal fluid, or blood. Therefore, the correct diagnosis depends upon routine bacteriological procedures.

Successful therapy of M. polymorpha meningitis has been accomplished by the use of penicillin and/or sulfonamides.

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Addendum

After this paper was submitted for publication, a case of meningitis due to M. polymorpha was reported by Olafsson et al.[15] Thus, a total of six cases of meningitis due to this organism are now recorded in the literature.

It is of further interest that Dexter and associates have recently called attention to what is probably a characteristic primary skin infection produced by M. polymorpha.[16]

REFERENCES

1. De Bord, G. G.: Organisms Invalidating the Diagnosis of Gonorrhea by the Smear Method, J. Bact. 38:119, 1939.

2. De Bord, G. G.: Descriptions of Mimeae Trib. Nov. with 3 Genera and 3 Species and 2 New Species of Neisseria from Conjunctivitis and Vaginitis, Iowa State Coll. J. Sc. 16:471, 1942.

3. De Bord, G. G.: Species of the Tribes Mimeae, Neisserieae, and Streptococceae Which Confuse the Diagnosis of Gonorrhea by Smears, J. Lab. & Clin. Med. 28:710, 1943.

4. Schuldberg, I. I.: Clinical and Pathologic Simulation of Meningococcic Meningitis: Report of Case with Necropsy, Am. J. Clin. Path. 23: 1024, 1953.

5. Deacon, W. E.: A Note on the Tribe Mimeae (De Bord), J. Bact. 49:511, 1945.

6. De Bord, G. G.: Mima Polymorpha in Meningitis, J. Bact. 55:764, 1948.

7. Townsend, F. M.; Hersey, D. F., and Wilson, F. W.: Mima Polymorpha as a Causative Agent in Waterhouse-Friderichsen Syndrome, U. S. Armed Forces M. J. 5:673, 1954.

8. Pike, R. M.; Schulze, M. L., and McCullough, M.: Isolation of Mima Polymorpha from a Patient with Subacute Bacterial Endocarditis, Am. J. Clin. Path. 21:1094, 1951.

9. Faust, J., and Hood, M.: Fulminating Septicemia Caused by Mima Polymorpha: Report of Case, Am. J. Clin. Path. 19:1143, 1949.

10. Cary, S. G.; Lindberg, R. B., and Faber, J. E., Jr.: Typing of Mima Polymorpha by a Precipitin Technique, J. Bact. 72:728, 1956.

11. Ransmeier, J. C.; Brown, H. E., and Davis, N.: Comparison of in Vitro Sensitivity of Freshly Isolated Pathogenic Bacteria to Terramycin and Other Antibiotics (Aureomycin, Chloramphenicol, Penicillin, and Streptomycin), J. Lab. & Clin. Med. 38:620, 1951.

12. Brooks, B. E., and Sanders, A. C.: "Unidentified" Gram-Negative Rods and the Tribe Mimeae, U. S. Armed Forces M. J. 5:667, 1954.

13. Lepper, M. H.; Dowling, H. F.; Wehrle, P. F.; Blatt, N. H.; Spies, H. W., and Brown, M.: Meningococcic Meningitis: Treatment with Large Doses of Penicillin Compared to Treatment with Gantrisin, J. Lab. & Clin. Med. 40:891, 1952.

14. Breed, R. S.; Murray, E. G. D., and Hitchens, A. P.: Bergey's Manual of Determinative Bacteriology, Ed. 6, Baltimore, Williams & Wilkins Company, 1948, p. 595.

15. Olafsson, M.; Lee, Y. C., and Abernethy, T. J.: Mima Polymorpha Meningitis: Report of a Case and Review of the Literature, New England J. Med. 258:465, 1958.

16. Dexter, H. L. T.; Glacy, J.; Leonard, J.; Dexter, M. W., and Lawton, A.: Skin Disease Due to Mima Polymorpha: Report of 2 Cases, A. M. A. Arch. Dermat. 77:109, 1958.

Benign Duodenocolic Fistula

Report of Autopsy Case Due to Peptic Ulcer and Review of Literature

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Introduction

Fistulous tracts are of unusual interest when they occur between the duodenum and the colon. Benign lesions are less common as an etiologic factor than malignant neoplasms. Rees,[1] in 1933, reported the first nonmalignant duodenocolic fistula and considered a ruptured typhoid ulcer to be the cause. Up to date a total of 21 examples have been recorded.[2-19] Other implied causations for this condition have been peptic ulcer, tuberculous lymphadenitis, ulcerative colitis, acute gallbladder disease, and even appendicitis. However, it appears that the same case has been cited by Krock[9] and Olson.[10] The patient presented by Blondeau[2] has been rejected because the death occurred without surgical proof of the diagnosis. Likewise, Case 2 of Garland and Wyatt[15] is open to question, since the sinus tract was not seen at operation, and was diagnosed later by roentgen studies. Thus it would appear that there are 19 authenticated cases of benign duodenocolic fistula in the literature.

Rosenqvist and Sjöberg,[18] although finding only 10 cases to 1955, feel that all should be published in the future, owing to the obscure etiology and various factors in therapy. Therefore, we wish to report an observation on a patient with this condition due to a peptic ulcer.

Report of Case

A 72-year-old widowed man was admitted to the Jennie Stuart Memorial Hospital on May 16, 1956, in an irrational state. No history was available from the patient. According to a brother, the patient had chronic stomach trouble for some 30 years, during which time soda had given relief. A severe diarrhea, without nausea or emesis, had developed in the last two weeks. Likewise, a recent weight loss of 30-40 lb. was estimated.

Examination revealed a thin, pale man who was irrational and acutely ill. The temperature was 97.8 F rectally, with a pulse of 100 and respirations of 24. The eyes, ears, nose, throat, and neck were negative for abnormalities. The chest had a few rales, and the heart revealed a tachycardia. An indefinite mass was palpated in the epigastrium but was considered to be an enlarged liver. A direct inguinal hernia was noted on the left side also. The impression was (1) peptic ulcer with anemia, (2) dysentery, (3) malignancy, to be ruled out, and (4) inguinal hernia.

Laboratory findings revealed on urinalysis, specific gravity of 1.010; trace of albumin; nega-

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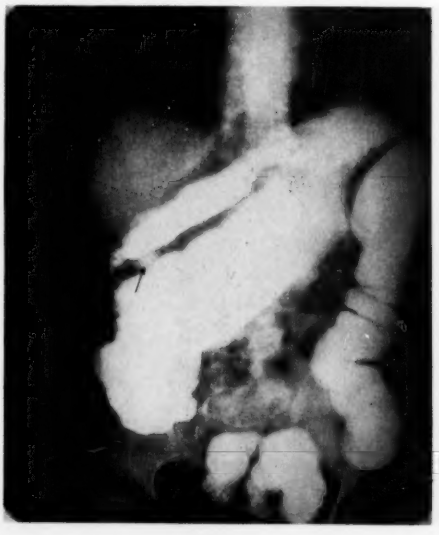
Fig. 1.—Photograph of x-ray of abdomen following barium enema with fistula (indicated by arrow) between first portion of duodenum and transverse colon just distal to hepatic flexure.



tive sugar reaction; 4-5 WBC, and a few hyaline casts. A blood cell count was recorded as 2,620,000 RBC, with hemoglobin value of 8 gm. per 100 cc., and the color index, 0.98. The white cell count was 15,350, with a differential of 91% neutrophilic granulocytes and 8% lymphocytes. A blood Kahn test was nonreactive. Gastric analysis was negative for free HCl after alcohol and histamine. A total of 10 degrees of combined acid was present, as well as 4+ mucus. Occult blood and numerous Trichomonas organisms were found in the feces, but it was negative for Amoeba.

On roentgen study with barium enema on May 17 (Drs. Gaither and Robert Coleman) it was noted that the opaque media filled the colon up to the midtransverse colon and then appeared directly in the stomach (Fig. 1). The distal end of the stomach appeared irregular, and the connection was thought to be at that point. The diagnosis of gastrocolic fistula, probably due to either malignant tumor or peptic ulcer, was made.

The course was downhill, with the patient being extremely restless. He had involuntary voiding and many large liquid stools daily. Later, drowsiness, inability to swallow food, and weakness prevailed. Diarrheal stools increased to every five minutes and contained completely undigested food several minutes after taken by mouth. The respirations increased to 30 as the temperature rose to 106 F rectally. The treatment consisted of Streptomagma (dihydrostreptomycin, kaolin, and pectin), camphorated opium tincture (paregoric), meperidine (Demerol), and soft diet. Surgical intervention was not considered because of the poor status of the patient. He died on May 21, 1956, five days after admission.

An autopsy limited to the abdomen was performed on May 21, 1956 (Drs. Gaither and Pautler). A 5 cm. fistula connected the first portion of the duodenum and the transverse colon just distal to the hepatic flexure. Numerous fibrous adhesions were present in the right upper quadrant of the abdomen, and an 8 cu. cm. accumulation of pus was noted in the lesser omental sac just posterior to the fistula (Fig. 2). The duodenal side of the fistula was firm but ulcerated. All other organs were normal, except for moderate atherosclerosis of the aorta. No neoplastic masses were seen in the abdomen. Histologic examination of the fistulous tract revealed marked amount of hyalin fibrous tissue involving the duodenum, with slight infiltration by a chronic exudate composed of lymphocytes, plasma cells, and macrophages. There was loss of mucosa, with a necrotic material composing the inner lining of the duodenum, typical of a peptic ulcer (Fig. 3).

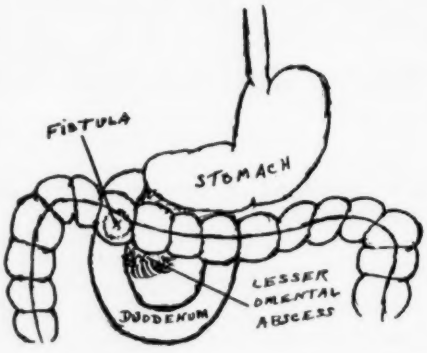


Fig. 2.—Diagrammatic sketch indicating the relation of the benign duodenocolic fistula and the lesser omental abscess.

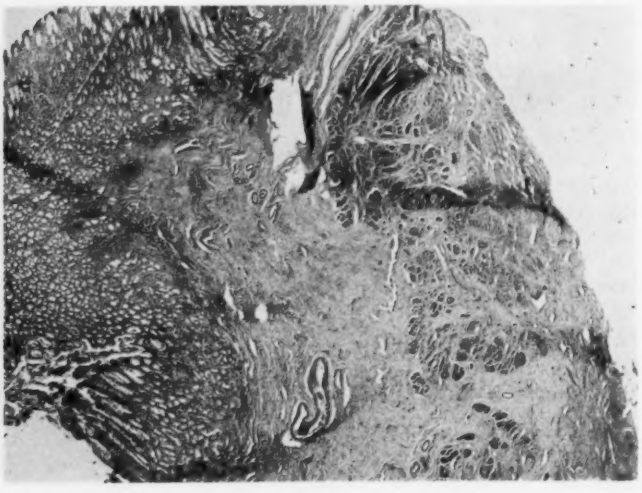


Fig. 3.—Photomicrograph of the chronic peptic ulcer of the first portion of the duodenum, at point of perforation into the colon. Note the large amount of collagenic scar tissue, chronic inflammatory exudate, and necrotic material. Hematoxylin and eosin; ×40.

Sections of the lesser omental sac revealed purulent exudate surrounded by fibrous tissue. No cytological or tissue changes of malignant tumor were found in any of the sections from the abdomen.

The final pathologic diagnoses were: (1) chronic (peptic) ulcer of first portion of duodenum with duodenocolic fistula, (2) lesser omental sac abscess, and (3) marked fibrous peritoneal adhesions.

Comment

A summary of 20 cases of benign duodenocolic fistula is presented in the Table, which is modified from Clayton and Thornton.[16]

The causative factors in these cases are multiple and may arise within the duodenum, within the transverse colon, or between the duodenum and colon. 1. Peptic ulcer of the duodenum constitutes about one-third of the total,[8] with an average age of 54 years and a 5:3 male-female ratio. 2. Tuberculous lymphadenitis has been suspected in four patients. The age grouping is in the forties, and the sex ratio is equal. 3. The next commonest condition has been chronic ulcerative colitis, with the three cases in the male sex and averaging about 20 years of age. Gallstones have been listed in two cases, with one each for typhoid fever, regional ileitis, and ruptured appendicitis. Rosenqvist and Sjöberg[18] feel that foreign bodies, i. e., needles and fishbones, should be seriously considered, since they could easily penetrate the curve of the duodenum and enter the colon. These authors feel that the location in the duodenum and the sex of the patients preclude ulcer etiology.

The duration of symptoms in the majority of patients (14) varied from 1 to 30 years. The commonest complaint was weight loss in 18 out of 20 persons, and this ranged up to 84 lb. Secondly, diarrhea, present in 16 people, was profuse, frequently with undigested food, and occasionally bloody. Vomiting occurred in 13 instances and was fecal in type on 5 occasions despite reports to the contrary.[20] Abdominal pain or cramps existed in about one-half of this series. Hershenson and Kirsner,[20] after finding only 32 cases of duodenocolic fistula due to carcinoma in the world literature, compared the symptomatology of the benign and malignant lesions. The only difference was that the benign cases tended to have less persistent diarrhea. McClinton[5] states that the HCl in the colon from the stomach produces hyperperistalsis, mucus secretion, and some blood in the stool. According to Rosenqvist and Sjöberg,[18] the diarrhea and emaciation are not due to the passage of undigested food through the fistula directly into the colon but rather the fecal contamination by regurgitation from the colon, resulting in a severe jejunitis. This produces rapid passage of intestinal contents and disturbed absorption (especially proteins), leading to hypoproteinemia and vitamin deficiency.

The diagnosis of duodenal-colic fistula was usually made by roentgen studies. The barium enema has been preferable to upper gastrointestinal manipulation and confirmatory in almost 75% of these cases (14). Surgical intervention is necessary to separate the benign and malignant causes.

Pathologic findings have usually been a fistulous tract arising from the transverse colon or hepatic flexure in almost all (18) cases and from the second portion of the duodenum in 50%. The tract varied from 1 to 5 cm. in diameter and was many centimeters in length. Histologic examination has found nonspecific fibrous tissue and chronic inflammatory exudate in all instances. They are lined by duodenal and/or colonic mucosa.

The management of these patients has been primarily a nutritional one and parallels that of gastrocolic or gastrojejunocolic fistula. Surgical procedure can only be done after correction of the anemia, hypoproteinemia, electrolyte (K) losses and avitaminosis. A high-protein high-vitamin diet and oral succinylsulfathiazole (Sulfasuxidine) is in order, and, as pointed out by Zollinger,[14] will increase weight gain, because succinylsulfathiazole produces a 30% to 90% rise in fat absorption. Ordinarily,

Summary of Authenticated Cases of Benign Duodenocolic Fistula

Author	Reported Etiology	Age	Sex	Abd. Pain	Emesis	Diarrhea	Wt. Loss, Lb.	Prob. Duration	Previous Surgery	Site of Fist.	Management	Course
Rees [1]	Ruptured typhoid ulcer	62	F	Yes	Yes	No	15	9 mo.	No	2d port. of duod. & trans. colon	Excision and closure	Well
Ormandy [2]	Chronic ulcerative colitis	31	M	Yes	Yes (Fecal)	Yes	70	1 yr.	No	1st port. of duod. & stomach to trans. colon	No surgery	Died; proven by autopsy
McPeak [4] (Case 1)	Ruptured duodenal ulcer	58	M	No	Yes	Yes	25	3 yr.	No.	Junct. 1st & 2d port. of duod. to hep. flex. of colon	Tract division & gastroenterostomy	Well
		Diagnosis by barium enema										
McPeak [4] (Case 2)	Ruptured duodenal ulcer	46	M	No	Yes	Yes	46	15 yr.	No	3d port. of duod. to trans. colon	Tract excision & bowel closure	Died; P. O. Abd. abscess
		Diagnosis by barium enema										
McClinton [5]	Ruptured duodenal ulcer	47	M	Yes	Yes (Fecal)	Yes	30	2 yr.	No	2d port. of duod. to trans. colon	Tract division & stump inversion	Well
		Diagnosis of ulcer by upper gastrointestinal series; diagnosis of fistula by barium enema										
Railton [6]	Duodenal ulcer	45	F	Yes	Yes	No	?	several weeks	No	1st port. of duod. to trans. colon	Devine exclusion gastrojejunostomy	Well
		Diagnosis of ulcer & fistula by x-ray										
Masters [7]	Regional ileitis	40	M	Yes	No	Yes	84	1 yr.	Yes; appendectomy, resection of ileum & colon	2d port. of duod. to trans. colon	Closure	Well
Ogilvie [8] (Case 1)	Tuberculous lymphadenitis	52	F	No	No	Yes	70	20 yr.	No	3d port. of duod. to hep. flexure of colon	Tract division & bowel closure	Well
Ogilvie [8] (Case 2)	Tuberculous lymphadenitis	54	M	No	Yes	Yes	Yes	9 yr.	No	3d port. of duod. to hep. flexure of colon	Tract division & bowel closure	Well

Olson [10]	? typhoid or duodenal ulcer	68	F	Yes	Yes (Fecal)	Yes	Yes	23 yr.	No	2d port. of duod. to hep. flexure of colon	Tract division & bowel closure	Well
					Diagnosis by barium enema							
Rife [11]	Penetrating duodenal ulcer	45	M	No	No	Yes	50	4 yr.	No	2d port. of duod. to trans. colon	Duod. closure resection of term. ileum to trans. colon	Well
Ransom [12] (Case 1)	Ulcerative colitis	28	M	No	No	Yes	Yes	?	Yes	Duod. to trans. colon	Duod. closure & subtotal colectomy	Well
					Diagnosis by barium enema							
Ransom [12] (Case 2)	Ulcerative colitis	12	M	No	Yes	Yes	Yes	?	No	Duod. to trans. colon	Duod. closure & subtotal colectomy	Well
					Diagnosis by barium enema							
Winfield [13]	? tuberculous lymphadenitis	Adult	M	No	No	Yes	Yes	1 yr.	Yes	3d port. of duod. to sigmoid colon	Tract excision & bowel closure	Well
					Diagnosis by barium enema							
Clayton [14]	Ruptured appendicitis	48	M	Yes	No	Yes	30	6 wk.	Yes	2d port. of duod. to cecum	Tract closure & drainage	Well
Neville [17]	Acute cholecystitis with gallstones	?	?	Yes	Yes (Fecal)	No	No	1 wk.	No	1st port. of duod. to hep flexure of colon	Tract closure & resection of hep. flexure of colon	Well
					Diagnosis by barium enema							
Rosenqvist [18] (Case 1)	? foreign body; ? tuberculous lymphadenitis	26	F	No	Yes	Yes	22	1 yr.	No	Junct. 2d & 3d port. of duod. to trans. colon	Tract division & closure; also appendectomy	Well
					Diagnosis of fistula by x-ray							
Rosenqvist [18]	Chronic cholecystitis with gallstones	61	M	Yes	No	Yes	11	2 mo.	No	1st port. of duod. to trans. colon	?	Well
					Diagnosis of fistula by x-ray							
Nash [19]	Probable ruptured peptic ulcer	39	F	Yes	Yes	No	20	2 yr.	No	2d port. of duod. to hep. flexure of colon	Duodenal closure; resection of hep. flexure of colon with anterior gastro-jejunostomy	Well
Present case	Perforated peptic duodenal ulcer	72	M	Yes	Yes (Fecal)	Yes	30–40	30 yr. 2 wk.	No	1st port. of duod. to trans. colon	No surgery	Died; confirmed by autopsy
					Diagnosis by barium enema							

ligation of the fistula and closure of the bowel has sufficed in the majority of patients. However, combinations of local bowel resections, shunts, and drainage have been employed.

The prognosis is generally excellent. Of the three patients who died, two were too ill for surgery and the other died from postoperative abdominal abscess.

Summary

A case of a benign duodenocolic fistula due to a perforated duodenal peptic ulcer and confirmed by autopsy is presented. The man died as a result of marked weight loss, dehydration, and emaciation, as no surgical intervention was deemed advisable.

A review of 20 authenticated cases in the literature is given. Etiology is multiform, but peptic ulcer heads the list. The diagnosis is made by barium enema, and malignant conditions, excluded by celiotomy. The problem of management is similar to gastrocolic fistula and is one of nutrition. Surgical division of the tract and bowel closure results in an uneventful course.

REFERENCES

1. Rees, C. E.: Duodenocolic Fistula with Incompetent Sphincter of Oddi, J. A. M. A. 100:496, 1933.

2. Blondeau, A. et al, cited by Clayton and Thornton.[16]

3. Ormandy, L., and Bargen, J. A.: Thrombo-Ulcerative Colitis Associated with Cologastric and Coloduodenal Fistulas, Proc. Staff Meet. Mayo Clin. 14:550, 1939.

4. McPeak, C. N.: Benign Duodeno-Colic Fistula, with Report of 2 Cases, Radiology 34: 343, 1940.

5. McClinton, J. B.: Non-Malignant Duodeno-Colonic Fistula, Canad. M. A. J. 1:434, 1944.

6. Railton, S. V.: Benign Duodeno-Colic Fistula, Canad. M. A. J. 59:267, 1948.

7. Masters, H.: Duodenal-Colic Fistula as a Complication of Regional Ileitis, J. Mt. Sinai Hosp. 15:264, 1948.

8. Ogilvie, H.: Non-Malignant Duodeno-Colic Fistula: Report of 2 Cases, Ann. Surg. 131:899, 1950.

9. Krock, F., in discussion on Ogilvie.[8]

10. Olson, J. D.: Unusual Gastrointestinal Fistulae, Am. Surgeon 17:335, 1951.

11. Rife, C. S.: Benign Duodenocolic Fistula, A. M. A. Arch. Surg. 62:876, 1951.

12. Ranson, H. K., in discussion on Rife.[11]

13. Winfield, J. M., in discussion on Rife.[11]

14. Zollinger, R., in discussion on Rife.[11]

15. Garland, J. G., and Wyatt, K., Jr.: Duodenocolic Fistula, Rocky Mountain M. J. 48:426, 1951.

16. Clayton, R. S., and Thornton, W. L.: Benign Duodenocolic Fistula: Review of the Literature and Case Report, Radiology 60:832, 1953.

17. Nebille, W. E.: Duodenocolic Fistula Due to Acute Cholecystitis, Am. J. Surg. 87:300, 1954.

18. Rosenqvist, H., and Sjöberg, S. G.: Duodeno-Colic Fistulas, Acta chir. scandinav. 109:293, 1955.

19. Nash, H. E., and Daland, E. M.: Benign Duodenocolic Fistulae, New England J. Med. 254: 1032, 1956.

20. Hershenson, L. M., and Kirsner, J. B.: Duodenocolic Fistula, Gastroenterology 19:864, 1951.

Salicylate Intoxication in an Adult

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In 1919 Lewis [1] published the first report of a case of acetylsalicylic acid poisoning in an adult in the English literature. Numerous reports of cases have been published since, but these do not reflect the true incidence, for records of the United States Bureau of the Census * reveal many more cases than the professional journals. We were able to collect from the literature in English reports of 115 instances, of which 15 were fatal. In 1952 there were 115 deaths in the United States due to salicylate poisoning of all types; 86 of them occurred in children less than 5 years old, and 41 of the deaths were due to acetylsalicylic acid.[3] Robin [4] reported the case of a patient who ingested 2500 grains of acetylsalicylic acid in a suicide attempt. The patient vomited four hours later and was lavaged three hours after vomiting, and so probably not all of the drug was absorbed. Nevertheless, this is a tremendous amount of salicylate and is the largest amount reported ingested with subsequent recovery.

We believe that the following case is of interest because of the large amount of drug consumed and the confusing clinical picture presented by the patient.

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* It is to be noted that an acute or chronic disease may be reported by the certifying physician as the primary cause of death and salicylate intoxication as a contributory cause. Nevertheless, "in accord with rules governing statistical handling of death certification" salicylate intoxication will be considered the primary cause in the official statistics of the Bureau of the Census.[3]

Report of Case

A 59-year-old man registered at the Mayo Clinic on Jan. 24, 1957, with a chief complaint of "herpes." The history revealed that the patient had suffered a myocardial infarction one year previously, for which he had been hospitalized one and one-half weeks. Since that time he had experienced occasional episodes of angina, with immediate relief brought about by glyceryl trinitrate (nitroglycerin).

Three weeks prior to his admission to the clinic, vesicles had developed in the patient's right cervical and occipital regions. The rash had cleared, but about 10 days prior to admission he had begun to suffer from severe paroxysms of pain affecting the right occipital region and extending to the right ear and shoulder. On several occasions the pain had precipitated substernal distress similar to the previous anginal attacks.

At the clinic, subsiding herpes zoster was found in the right occipital area. No abnormalities of the heart or lungs were noted on physical examination, and results of the remainder of the examination also were within normal limits. The patient was hospitalized for further observation and treatment. Acetylsalicylic acid, acetophenetidin, and (Emperin Compound), 13 grains (0.84 gm.), and codeine, ¼ grain (0.016 gm.), were prescribed for the paroxysms of pain, and glyceryl trinitrate as needed for substernal distress.

Initial laboratory findings were as follows: Urinalysis, acid reaction; albumin, Grade 2; sugar, Grade 1; casts, occasional; erythrocytes, Grade 1; leukocytes, Grade 1. Blood studies: hemoglobin, 16.6 gm. per 100 cc.; erythrocytes, 4,860,000 and leukocytes, 8500 per cubic millimeter; urea, 42 mg. per 100 cc. Chest roentgenogram: linear fibrosis at the base of the left lung and a Ghon lesion. Electrocardiogram: sinus tachycardia, left axis deviation, and changes of a healed myocardial infarction.

Initial hospital examination disclosed that the patient was anxious and tense and had marked cutaneous hyperalgesia over the face and neck at the site of the previous vesicles. He was apprehensive that examination might aggravate the pain and was uncooperative. Hyperpnea was noted and was thought to reflect anxiety. A bottle of acetylsalicylic acid was noted among his possessions, and, in reply to direct questioning, he stated

that he had taken 2 to 4 pills a day for relief of pain, but with little effect. That evening the patient became extremely agitated, confused, and disoriented, and attempted to leave the hospital in his pajamas. He stated he was having a "heart attack" and was about to die. Examination revealed his blood pressure to be 112 mm. of mercury systolic and 72 diastolic, pulse 140 per minute, and respirations 24 per minute. His perspiration was profuse, and his lips, faintly cyanotic. The lungs were clear, and the heart sounds were normal. He was placed in an oxygen tent and given morphine, 10 mg. subcutaneously, for relief of anxiety and pain. He appeared more comfortable and spent a fairly quiet night.

The following morning it was noted that left hemiplegia had developed. The patient was confused and hyperpneic and continued to perspire profusely. A second electrocardiogram showed no change from the initial tracing. Several hours later he became comatose and within an hour appeared moribund. At this point the possibility of salicylate intoxication was entertained, and a search of the patient's room revealed the previously noted acetylsalicylic acid bottle to be empty. The blood salicylate concentration was tested and was found to be 61 mg. per 100 cc. The carbon dioxide-combining power was 11.7 mEq.; serum potassium, 4.3 mEq. and serum chlorides, 109.4 mEq. The concentration of blood sugar was 136 mg. per 100 cc. The prothrombin time was 24 seconds. Urinalysis yielded the same findings as on admission. Because of the duration of the signs and symptoms it was presumed the patient was in a state of metabolic acidosis, and therapy was started with 1000 cc. of M/6 solution of sodium lactate administered intravenously at a rate of 80 drops per minute. Chvostek's and Trousseau's signs were not present at the start, and there was no evidence of tetany during the intravenous infusion. When the first infusion was completed, the carbon dioxide-combining power had risen to 19 mEq. and a second similar infusion was begun. Four hours after the start of the initial infusion the patient was no longer comatose and responded to simple questions and commands. The diaphoresis and hyperpnea had diminished greatly. He improved rapidly during the next four hours. The salicylate level the next day was 39.7 mg. per 100 cc. of blood, and on the third day it was 15.5 mg.

The fasting blood sugar on the third day was 179 mg. per 100 cc., and glycosuria was present. After three days of observation, the fasting blood sugar was 135 mg. per 100 cc., and treatment for that was begun with a dose of 10 units of isophane (NPH) insulin daily. Recovery was uneventful except for some persistence of the left hemiplegia. This improved considerably with physical therapy, and at the time of dismissal there was only slight residual weakness of the left arm and the gait was essentially normal. The patient was free of pain except for occasional minor twinges and required no analgesics following his return to consciousness.

At examination two months later the patient reported that he had continued to take 10 units of insulin daily and to follow the prescribed diet. The fasting blood sugar amounted to 135 mg. per 100 cc. No family history of diabetes could be elicited.

He was questioned in detail about the amount of acetylsalicylic acid consumed. He stated that for 10 days, beginning 2 weeks prior to admission, he had taken acetylsalicylic acid in the amount of 10 to 15 tablets daily. In the four days prior to arrival he had consumed an estimated total of 600 five-grain tablets, and on the day of admission to the hospital he had consumed one hundred tablets from the previously noted bottle. The patient estimated the total amount as 700 five-grain tablets over the five-day period. At no time had he experienced nausea, vomiting, or tinnitus. The patient had noted no further substernal distress, and his recovery of muscle strength was virtually complete. He was dismissed with the prescription for diabetic diet and insulin unchanged.

Comment

Symptoms and Diagnosis.—The symptoms of salicylate poisoning have been documented well. They consist primarily of tinnitus, headache, deafness, nausea, vomiting, hyperpnea, profuse sweating, and erythema. The symptoms of mental confusion and irrational behavior, so well exhibited in this patient, have been termed "salicylate jag." Graham and Parker[5] correlated the various toxic manifestations with plasma salicylate levels in rheumatic fever patients receiving sodium salicylate. They found that vomiting, hyperpnea, and sweating occurred at mean salicylate levels of 28.2, 32.8, and 36.6 mg. per 100 cc., respectively. Confusion and excitement occurred at mean levels of 46.9 and 48.1, and pulmonary edema, at 49.4. There was a wide range of levels at which various symptoms appeared, demonstrating much individual variation in susceptibility to the drug.

The chief problem of differential diagnosis to be considered is that involving diabetic acidosis. The hyperpnea and the

presence of acetone and reducing substance in the urine could be features in the picture of diabetic acidosis, and the low combining power of serum carbon dioxide further suggests this diagnosis. If a history of the ingestion of salicylates can be obtained, the diagnosis becomes obvious; if not, the finding of a normal or only slightly elevated blood sugar immediately makes this diagnosis of diabetic acidosis suspect and the possibility of salicylate intoxication should be considered.

Respiratory Alkalosis and Metabolic Acidosis.—The salicylates induce primary hyperventilation, believed to be due to direct action on the respiratory center. The hyperventilation causes a respiratory alkalosis with a reduction in the carbon dioxide-combining power. As a result of the loss of carbon dioxide from the lungs, bicarbonate is excreted by the kidneys in order to maintain the usual ratio of carbonic acid to bicarbonate, and thus serum bicarbonate is diminished. Farber and co-workers [6] gave a total of 12 gm. of acetylsalicylic acid to each of 10 men over a period of nine hours. An average peak level of 39 mg. per 100 cc. was attained two hours after the last dose. The average increase in pH of the venous blood amounted to 0.06; the carbon dioxide tension decreased by 11 mm. of mercury, and the bicarbonate decreased by 2.8 mM. per liter. The maximal displacement occurred four hours after the last dose. Thus, with therapeutic doses of salicylate, mild respiratory alkalosis is induced.

The respiratory alkalosis is followed by the development of metabolic acidosis, although the mechanism of this change is not known. Some authors believe it is started by a specific action of salicylate on carbohydrate metabolism in the liver, with resultant rapid depletion of glycogen. Ketosis then results and, because the bicarbonate reserve has been diminished already, it rapidly becomes severe. The time required for acidosis to develop varies greatly with individual patients, but in infants it develops very quickly. The acidosis provides a further stimulus for hyperventilation and, if allowed to continue, soon becomes uncompensated with resultant death of the patient.

Treatment.—Until the 1955 report by Schreiner and co-workers,[7] the treatment of salicylate poisoning was largely symptomatic. Gastric lavage should be performed in the hope of recovering some of the ingested salicylate. In the alkalotic stage fluids should be administered in the form of glucose in water. Small doses of sodium bicarbonate are recommended by some authors because bicarbonate increases the renal excretion of salicylates and also prevents too great a lowering of the bicarbonate reserve. The danger of large doses would be the aggravation of the alkalotic state, and some authors recommend that no bicarbonate be given until a state of acidosis exists. Once the patient has become acidotic, intravenous injection of sodium lactate is the preferred form of therapy. This was first introduced by Williams and Panting [8] in 1937 and since that time has been standard treatment for salicylate poisoning. The change in our patient's condition after the administration of sodium lactate was quite dramatic and has been noted in many cases previously.

Schreiner and co-workers [7] reported a case of acetylsalicylic acid poisoning treated by dialysis with the artificial kidney. The initial salicylate level was 90 mg. per 100 cc. and was reduced by 57 mg. per 100 cc. by dialysis for six hours. If the artificial kidney is available, this certainly constitutes the procedure of choice for severe salicylate poisoning; it may be life-saving in many such cases. The presence of recent hemiplegia with possible cerebral hemorrhage contraindicated its use in our patient.

Complications.—Glycosuria and hyperglycemia have been frequently noted in salicylate toxicity. In some instances the report of glycosuria may have been due to the presence of salicylate in the urine, since salicylate is a reducing substance for

copper-containing reagents. In other instances, however, care has been taken to make certain the reducing substance was glucose. Sevringhaus and Meyer [9] reported hyperglycemia in an adult nurse poisoned by methyl salicylate whose glucose tolerance curve remained definitely abnormal eight days after recovery but was normal again two weeks later. Silverman and Piccolo [10] speculated that the hyperglycemia may be due to damage to the hypothalamic region by the salicylate. So far as we know, ours is the first report of a case of salicylate poisoning following which permanent diabetes mellitus developed. The occurrence is in all likelihood coincidental, but in view of the known hyperglycemic effects of salicylates it seems of interest. It is not possible to exclude the possibility that the patient had an abnormality of carbohydrate metabolism before the present illness began, but no record of this had been made during his previous hospitalization for the myocardial infarction.

Cerebral infarction also developed in our patient. Numerous autopsy reports have tabulated petechial hemorrhages in the pericardium, lungs, brain, spinal cord, and mesentery in salicylate poisoning. Whether the infarction was due to a small hemorrhage occurring as a result of the salicylate toxicity or is a coincidental occurrence is impossible to state, but probability would favor the latter explanation. The prothrombin time was never elevated enough that hemorrhage was considered likely.

Finally, this patient had a well-documented postherpetic neuralgia. In a number of reports of salicylate toxicity, however, scalp paresthesias and pain have been mentioned as prominent symptoms. It is entirely possible that the toxicity greatly increased the pain after the patient became toxic, leading him to take more acetylsalicylic acid and thus continue a vicious cycle. The almost complete disappearance of pain following recovery may have been due in part to the elimination of salicylates.

Summary

A case of severe salicylate intoxication in an adult with subsequent recovery is reported with brief comment on the symptoms, differential diagnosis, metabolic derangement, and treatment.

The glycosuria and hyperglycemia of severe salicylate intoxication are mentioned. To our knowledge this is the first reported case following which the patient developed permanent diabetes mellitus. We believe the occurrence to be coincidental but of interest.

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REFERENCES

1. Lewis, F. W.: A Case of Aspirin Poisoning, Lancet 1:64, 1919.

2. Gross, M., and Greenberg, L. A.: The Salicylates: A Critical Bibliographic Review, New Haven, Conn., Hillhouse Press, 1948, p. 157.

3. Precautions Regarding Salicylates, Including Aspirin, Council on Pharmacy and Chemistry, J. A. M. A. 158:831 (July 9) 1955.

4. Robin, A. A.: Case of Aspirin Poisoning, J. Ment. Sc. 97:214-216 (Jan.) 1951.

5. Graham, J. D. P., and Parker, W. A.: Toxic Manifestations of Sodium Salicylate Therapy, Quart. J. Med. 17:153-163 (April) 1948.

6. Farber, H. R.; Yiengst, M. J., and Shock, N. W.: Effect of Therapeutic Doses of Aspirin on the Acid-Base Balance of Blood in Normal Adults, Am. J. M. Sc. 217:256-262 (March) 1949.

7. Schreiner, G. E.; Berman, L. B.; Griffin, J., and Feys, J.: Specific Therapy for Salicylism, New England J. Med. 253:213-217 (Aug. 11) 1955.

8. Williams, S. W., and Panting, R. M.: Treatment of Aspirin Poisoning by Intravenous Sodium Lactate Solution, Brit. M. J. 1:550-552 (March 13) 1937.

9. Sevringhaus, E. L., and Meyer, O. O.: Glycosuria and Recovery Following Methyl Salicylate Poisoning, Ann. Int. Med. 3:1147-1148 (May) 1930.

10. Silverman, I., and Piccolo, P. A.: Oil of Wintergreen Poisoning, Bull. New England M. Center 4:172-176 (Aug.) 1942.

Reviews of Internal Medicine

Infectious Diseases

Annual Review of Significant Publications

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In the past year, as usual, a number of significant contributions were made to knowledge in the field of infectious diseases. Unfortunately, there was little evidence of more discriminate or restrained prescription of the prodigious amounts of manufactured antimicrobics. As one result, and despite some opinion to the contrary, the problem of antimicrobic resistance acquired by staphylococci and other bacteria has intensified, as indicated by the number of pertinent publications. Controversy also continues, even in official circles, over the value of BCG vaccine. Antipoliomyelitis vaccine seems to have accomplished much in reducing the severity of poliomyelitis, but some skeptics prefer to delay its appraisal. Poliomyelitis-like epidemic infections and their relationship to ECHO, Coxsackie, and other viruses held much attention. Of greatest public interest was the emergence of a new variant of influenza A virus, unfortunately named Asian, that caused a world-wide pandemic mostly of mild disease. Alarming publicity incited much unnecessary anxiety. Forewarning of the spread of infection provided opportunity to test the facilities for the prompt manufacture, distribution, and administration and the value of enormous amounts of a specific vaccine.

Antimicrobics

In 1955, a total of 1200 tons of antimicrobics were made, valued at over $1,000,000,000.[1] According to Welch, 440 tons of penicillin were made last year and 150 preparations of it are on the market. An estimated 10% of people are apt to be sensitive. In a survey of 1706 samples of milk, 6% contained penicillin; the highest amount was 550 units per 1000 cc. Other samples contained streptomycin, bacitracin, and tetracycline, presumably originating from cows treated with these drugs, and all may be allergenic.[2]

Intense commercial competition is evident in the amount of expensive, eye-catching, psychologically enticing, and sometimes misleading circulars mailed in thousands to physicians and reproduced in medical journals. It would be better to economize on advertising propaganda and reduce the price of the products. According to a newspaper report, the Federal Trade Commission is investigating the reasons for the high cost of antimicrobics other than penicillin.[1]

Physicians should develop a greater degree of sales resistance and prescribe drugs by their official names in correct amounts when they are needed. About one in four prescriptions filled at pharmacies call for antimicrobics. Tabulation made of patients visiting a dispensary over a four-year period revealed that 92% had received antimicrobics. On 52% of occasions, therapy was considered unwarranted.[3] More critical appraisal may have shown a higher percentage. Among 252 members of the nursing staff of a hospital, 28% had received sulfonamide drugs and 16% had had reactions; 76% had received penicillin for some minor infection and of these 15% had reactions. Seven per cent had received streptomycin, and twenty-three per cent, one of

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the tetracyclines. Of the whole group, 31% had had two antimicrobics; 13%, three; 2%, four, and 2%, five and six.[4] Considering the small percentage of all infections amenable to antimicrobic therapy, these figures indicate misguided medical judgment. Antimicrobics are of no value in the treatment of the great majority of infections, namely, those caused by viruses.[5]

Antimicrobial Combinations. — Adverse comment was directed at packaged combinations of antimicrobials prepared by manufacturers.[6-9] Combinations are needed only for tuberculosis and for rare circumstances, as, for example, subacute bacterial endocarditis, some staphylococcal infections, brucellosis, and certain mixed infections. There is no justification for giving penicillin and streptomycin together almost as a routine procedure.[10] Combination of penicillin with erythromycin, oleandomycin, or tetracycline yielded less antibacterial effect against staphylococci, streptococci, and pneumococci than that exhibited by the same total amounts of the single agents.[11] Levitt detected no evidence of synergism.[12] Combination of erythromycin and chloramphenicol failed to reveal any enhanced activity over that expected from either agent alone. However, such combinations at times may be of value.[13,14]

Garrod saw no need for the continued existence of oxytetracycline, chlortetracycline, and tetracycline when one of them serves the purpose.[15] Tetracycline was effective in curing 18 of 19 children with meningitis caused by Hemophilus influenzae, Neisseria meningitidis, and Diplococcus pneumoniae.[16]

Pleas for restricting the use of novobiocin and erythromycin for the treatment solely of staphylococcal infections were largely ignored. Their indiscriminate use is leading to the appearance of resistant strains. Novobiocin was found to be unsatisfactory in the treatment of hemolytic streptococcal infections, and many dermal eruptions occurred.[17] Erythromycin was effective in controlling infections caused by hemolytic streptococci, pneumococci, gonococci, and meningococci. Both agents should be reserved for the control of penicillin-resistant staphylococci.[18]

Oleandomycin and spiramycin are sufficiently inferior to erythromycin to warrant their rejection.[14] A new antimicrobial, streptovaricin (Dalacin), has five components. It is active against tubercle bacilli and Gram-positive bacteria and does not induce cross resistance to streptomycin or other agents.[19]

Penicillin.—Rapid intravenous injection of penicillin combined with intramuscular injection of procaine penicillin and probenicid given orally caused the amount of penicillin in the blood to increase twofold to eightfold over amounts without probenicid.[20] Probenicid caused fatal hepatic necrosis in one patient.[21] Except in unusual circumstances when penetration of dense areas is needed, it is uncertain how much advantage is gained by increasing the dosage of penicillin from 1,000,000 units (600 mg.) to 100,000,000 units (60,000 mg.). Six of forty-six patients whose γ-globulin was normal in amount were said to have responded better when γ-globulin was given in addition to antimicrobials.[22]

Allergic Reactions.—Penicillin given prophylactically to 13,000 persons caused allergic reactions in 68 (0.5%). Fifty-two reactions followed intramuscular injection, and sixteen followed oral administration. Fifty had received penicillin previously. Twenty-five had erythema multiforme, and the rest were less severely sick. Arthralgia occurred in 41, and fever, in 34. For treatment, an antihistaminic agent, corticotropin, and a placebo were used. Those who received a placebo recovered as quickly as the others.[23] Penicillinase, an enzyme that destroys penicillin, was used to treat allergic reactions in 42 patients. The results were hard to judge. In some, the symptoms worsened; others were relieved. Similar results followed the administration of a placebo.[24] Despite these equivocal results, penicillinase is on the market as Neutrapen.

According to report at the Fifth Antibiotics Symposium in Washington, there

were 1072 life-threatening reactions and 1925 less serious ones observed in 5431 hospitals between 1953 and 1956. Among 809 instances of anaphylaxis, there were 72 deaths.[25]

Smith used solution of penicillin dropped into a dermal scratch and on the conjunctiva to test patients for hypersensitivity. A prompt reaction indicated hypersensitivity.[26] In my experience, these methods were untrustworthy in detecting hypersensitivity to antipneumococcal serum.

Penicillin caused disruption of the walls of Escherichia coli and extrusion of their contents.[27] In an attempt to explain this antibacterial effect, it was suggested that uridine pyrophosphase N-acetylamino sugar peptide is a biosynthetic precursor of the bacterial cell wall. Its accumulation in staphylococci exposed to penicillin follows interference by penicillin with normal biosynthesis of the wall. Information of this sort may lead to the discovery of agents to attack viruses as well. Search is under way for specific inhibitors of nucleic acid synthesis to attack virus bodies without harm to the cells of the host.[28]

Phenoxymethyl penicillin has been synthesized. Eventually it may be possible to prepare a product insusceptible to penicillinase[29] or products less apt to sensitize patients.

Antimicrobics Used Prophylactically.—Antimicrobics have a limited value when used to prevent infections. They oppose invasion by hemolytic streptococci, meningococci, and gonococci. Tetracycline or neomycin given orally reduce the number of enteric bacteria prior to intestinal surgery.[30] On the other hand, in Griffiths' experience penicillin failed to prevent postoperative infections. In fact, more infections occurred in treated patients than in control subjects.[31] Similar observations were made by Kapp, who condemned the routine use of antimicrobics for prophylaxis in surgical practice.[32]

As reported on previously by others, during infection of the respiratory tract more bacterial complications and longer-lasting illness occurred among children treated with antimicrobials, especially chlortetracycline, than among those who received no medication.[33] According to Petersdorf and his coworkers, antimicrobics given to comatose patients failed to prevent infections. Pulmonary complications were more than twice as common in treated patients.[34] Antimicrobics have no value in preventing pulmonary infection during measles, in poliomyelitis patients with tracheotomy, or in urinary tract infections from indwelling catheters.

Antimicrobics and Mycoses.—Antimicrobics and steroid therapy incited secondary fungal infection in 13 patients. Distinction was made between proliferation of funguses on the mucosal surface after antimicrobial therapy and invasion of tissue when steroids also were given.[35] The incidence of infections with Torulopsis glabrata and with Candida albicans seems to be increasing in patients treated with antimicrobics for other conditions.[36]

To account for mycotic infections during therapy, it was thought that the drugs stimulated the growth of funguses or that their growth was permitted by the elimination of competing bacteria. There may be another reason. Disintegration of C. albicans by other means released a toxic agent which, when combined with chlortetracycline, was toxic for mice.[37] Trichomycin and Acinitrazole both were ineffective in the treatment of trichomonal infections.[38]

Viral Diseases

Viral Infections of the Respiratory Tract

Infections of the respiratory tract caused one-third of illnesses among university students and had an incidence of 171 cases per 1000 in a six-year period. Bacteria, chiefly hemolytic streptococci, were the cause in 16% of cases, and infectious mononucleosis accounted for 20%. Among students sick enough to be admitted to the hospital, adenoviruses Types 1, 3, and 4 were present in 2%; influenza virus, in 3.4%, and hemo-

lytic streptococci, in 8.3%. Viral pneumonia occurred in 5.8%, and bacterial pneumonia, in 3.8%. In 84% of patients tested, the cause of infection was not found. Because of the low incidence of adenoviral disease, Evans did not favor the use of specific vaccine.[39]

It is impossible clinically to differentiate certain viral infections of the respiratory tract, even during epidemics. A large outbreak of mild disease in a community was suspected to be of influenza B. Yet evidence of that infection was found in only seven patients. The actual cause was not discovered, and adenoviruses were not implicated.[40]

A virus named 2060 or JH, present in nasal washings of patients with mild disease, may be one of the causes of "colds."[41,42] Specific antibody appeared in the blood of patients and of other persons in the community. A vaccine prepared from the virus was said to prevent infection. According to editorial comment, harm may be done by premature reports of successful vaccination. Immunity probably is of short duration, and vaccination may be futile.[43]

In the face of previous authoritative advice to the contrary, autogenous vaccines and antimicrobics again were used with reported success in the treatment of colds. On the assumption that secondary bacterial infections make the viral disease worse, vaccines made from the nasopharyngeal flora greatly reduced the progression of colds into "full colds" as compared with control patients. No attempt was made to identify the bacteria.[43a,43b] However, there is no acceptable evidence that bacteria become invasive in more than 0.1% to 0.2% of colds or that vaccines made from oral flora have any specific immunizing value. On the same theory, the same author also found that minute doses of 15 mg. of tetracycline drugs given orally twice daily similarly prevent the development of full colds. Viridans Streptococcus was present in a high percentage of patients; a few had hemolytic streptococci, and, surprisingly, staphylococci were almost absent.[43a,43b] The reports were publicized in a popular lay magazine [43c] and no doubt will be widely accepted as conclusive.

For years we have been warned against using amounts of antimicrobics too small to be effective, because they do no good, they are apt to sensitize patients, and they may lead to superinfection with resistant bacteria. It is questionable whether persons should be subjected to these risks for minor self-limiting colds.

A multidrug commerical product, Pen-Vee-Cidin, containing penicillin, acetophenetidin, and three other compounds, also is widely advertised. It is supposed to give symptomatic relief and protection from secondary bacterial infection and to counter depression, fatigue, fever, emotional unrest, and cough. Nothing seems to have been omitted except some steroid hormone, terpin hydrate, and acetylsalicylic acid.

Adenoviral Disease.—Several epidemics of pharyngoconjunctival fever caused by adenoviruses Types 3, 7, and 14 were observed among civilians in England. No victims were said to have had viral pneumonia. Roentgenograms were not made routinely, but in two patients evidence of pulmonary infiltration was present after recovery.[44] The authors regarded pneumonia as a complication rather than as an integral part of the disease, which it is. Penicillin, chlortetracycline, and sulfadimidine were administered but, as expected, without effect. Suggestion was made that nontuberculous juvenile bronchiectasis is associated with adenoviral infection. Serologic evidence of viral activity was demonstrated in 11 of 18 patients, and the virus was isolated from 1.[45] It is uncertain whether the virus was the cause or a commensal or if bronchiectasis antedated the infection.

Six volunteers were given inoculations intramuscularly of viruses Types 3, 4, and 7 grown in human embryo intestinal cells in tissue culture. The danger of the possible presence of hepatitis virus in the cells was considered, but poliomyelitis virus was not. Within a few hours, three volunteers had

a severe primary toxic reaction, and after a few days all had respiratory tract disease. In one it was insignificant; in two it was mild, and in three, moderately severe but without pneumonia. In contrast with the naturally occurring disease and in volunteers infected by way of the conjunctiva or nares, the viruses were not recoverable from these sites after intramuscular inoculation. Antibody appeared much sooner, however, suggesting the practical use of the procedure for immunization.[46]

Further study of the value of vaccination against Types 4 and 7 infections revealed a 98% reduction in the number of patients sick enough to require care in a hospital. The success of vaccination in ameliorating attacks saved much expense. There was no significant reduction in the number of victims with mild attacks, but many infections probably were of other viral origin.[47]

Other Studies.—A colorimetric method to assay neutralizing antibody against adenoviruses in HeLa tissue culture also provided means for determining the type of virus.[48] A hemagglutination test is said to be superior to the complement-fixation test and simpler to perform to detect adenoviral infection, but it is not type-specific.[49] Cultures of cells infected with Type 4 virus contained increased amounts of lactic, pyruvic, acetic, and ketoglutaric acids. The cells also utilized an increased amount of glucose.[50]

Influenza.—A statistical study revealed a progressive decline in the mortality rate from "influenza and pneumonia" since 1900. It reached its nadir in 1953-1954.[51] Official statistics grouping influenza with bacterial pneumonias, however, are unsatisfactory and confusing. They are separate diseases. Furthermore, before and after influenza viruses were discovered, many minor respiratory tract diseases and others with only aching and fever were wrongly reported as influenza. The mortality rate of influenza A, B, C, or D rarely exceeded 1%; that of secondary bacterial pneumonia was, of course, much higher but has been improved by antimicrobic therapy. The published mortality statistics chiefly reflect fatalities from bacterial pneumonias. Even these seldom are separated into etiologic entities as they should be.

Antibodies for influenza A and B were present in about 3% of a population before and after epidemics of both kinds. The incidence rose to about 12% during the epidemics but fell to 2% six months later. There was no evidence of preepidemic seeding of the viruses to account for the outbreaks, since a rise in the incidence of reactors lagged behind the onset of the epidemics. Either a new strain was introduced[52] or changes in the population allowed a resident virus to become invasive. The persistence of antibody in a few persons suggested that the viruses lie dormant in carriers. This was shown to occur after a child was infected by contact with an asymptomatic carrier.[53]

Four types of virus—A, B, C, and D—each are separated further into sets or families. A new variant of Type A virus named Far East or Asian emerged in May, 1957.[54] The subject was summarized editorially.[55] Type D (Sendai) influenza occurred in Scotland.[56] Cases also appeared in England, and viral pneumonia was present in a number of them. The infection was indistinguishable from that caused by other influenza viruses.[57] Influenza viruses A, B, and D caused a small proportion of minor respiratory tract diseases in Glasgow. Antibodies were difficult to detect in infants.[58] The relationship of D virus to mumps virus is under investigation. The "croup" virus of Channock is related serologically to mumps virus but not to influenza D.[59]

"Asian" Influenza.—The new variant of virus Type A caused a world-wide pandemic of disease called Asian influenza. The name, memory of the 1918 pandemic of "Spanish" influenza, and sensational publicity created much unnecessary apprehension and near panic. On the other hand, it was the first occasion on which advance information of a rapidly spreading disease was given. This warning made it possible

to vaccinate large numbers of persons beforehand. Many authorities, however, saw no cause for alarm and opposed mass vaccination.[60] It is unwise to cry "wolf, wolf" when there is no wolf. The disease probably affected more persons than in other recent epidemics of influenza, in places involving 20% or more of the population, but previous epidemics did not receive such intense statistical attention. In general it was mild and not much different from those in other years, and the few fatalities reported were mostly in infants, in the aged, and in debilitated persons, as expected. In one report of 46 fatal cases, pneumonia was present in 37 and preexisting chronic cardiac or pulmonary disease in 35.[61] More than half of the deaths in Holland were caused by staphylococcal superinfections, many of them resistant to penicillin. Other cocci and H. influenzae rarely were isolated. Influenza virus but no bacteria were in the pneumonic lungs at necropsy in nine patients with mitral stenosis.[62] Secondary bacterial pneumonias rarely occurred. Staphylococcal pneumonia was the most serious form. Vaccine gave a degree of protection against influenza [63,64] but occasionally caused reactions with symptoms severer than those of the disease. In one report of 57 vaccinated persons, 14 had fever, 54 had pain in the extremities, 18 had local swelling, and 42 had pain at the site of injection.[65] Vaccination against influenza still is in the experimental stage and should be so regarded.

Influenza Vaccine: Field trials of vaccine were made in England. Vaccines made from strains isolated in 1955-1956 gave the same degree of protection as those made earlier. The absentee rate of workers was lowered about 30% to 40%, as compared with controls. Vaccine with oily adjuvants gave no evidence of protection after 12 months. Influenza B vaccine failed to protect against a B virus infection. Untoward reactions to vaccination were excessive, and 0.5% were severe.[66] The frequence and severity of reactions are related to the amount of virus in the vaccine. Russian investigations summarized by Smorodintsev (*Problems Virol.* 2:65, 1957) showed that vaccination reduced the incidence of influenza by 3.5 times. A′ and D viruses were isolated in an epidemic in Vladivostok.

I have found no report of postmortem studies of the upper respiratory tract on persons who died of other cause while having influenza or other similar disease. It would be of interest to know if pathologic differences characterize the various entities now established. Fotin inspected the mucous membranes of patients with influenza. About half showed acute hyperemia, edema, and an exudate, like the changes seen in vasomotor rhinitis. In the rest the changes were minimal. The membrane was dry and cyanotic. In his view, the virus acted on the nervous system, causing peripheral vascular paralysis and collapse.[67] More likely the virus injures the mucous membrane directly. In other studies, electron microscopic examination of the mucosa during influenza viral infection of ferrets visualized cellular destruction, replacement, and regeneration.[68]

Croup.—Infantile croup seldom is associated with bacteria. Studies suggest a newly recognized myxovirus as a cause. The virus, called CA (croup associated), evoked a spongy cytopathogenic change in tissue cultures. Blood from victims specifically neutralized the virus.[69]

Viral Pneumonia.—Antibody against PAPV virus isolated from patients with a form of viral pneumonia appeared about the second week after the onset of illness and persisted more than a year. It was not related to cold agglutinin or to MG agglutinin. Eight viruses similar to PAPV were derived from patients during several seasons.[70]

Viremia during a number of viral diseases may give rise to specific pneumonia. A patient with viral pneumonia had herpes zoster. Inflamed vesicles in the bronchus presumably of herpetic origin were visualized by bronchoscopy.[71] In another case, pneumonia appeared 15 days after cat-scratch disease began.[72] On weak evidence,

French observers reported a form of viral pneumonia during poliomyelitis, presumably caused by the same virus.[73] The nature of the disease as described leaves doubt of the diagnosis.

Viral Nephritis?—A number of patients were observed with acute nephritis not caused by hemolytic streptococci. Adenoviral respiratory tract infections were rampant at the time, and one patient had viral pneumonia. The period between the respiratory tract infection and the nephritis did not exceed five days, which is shorter than after streptococcosis. The signs, symptoms, and histologic renal changes were relatively mild. Nephritis of viral origin was suspected.[74]

Poliomyelitis

A study revealed a decline since 1915 of about 90% in the death rate and probably in the incidence of paralytic attacks in children less than 15 years old.[75] The statistical decline was ascribed to natural immunization and better care, but there are other reasons as well, such as diagnosis of mild nonparalytic cases. It is hard to see why natural immunization should be effective after 1915 and not before that time. Poliomyelitis is not a new disease, and immunizing epidemics certainly occurred in the past.

Poliomyelitis is widespread in Saudi Arabia, where 75% of persons tested had antibody for one of the three types of virus.[76] In Israel, 95% of the children had antibodies.[77] In an epidemic in England, of 121 cases of paralytic disease, 7 had encephalitis. Virus was isolated from the feces of five, and serologic tests gave positive results in six. Evidently, poliomyelitis may appear as an acute cerebellar ataxia or acute encephalitis.[78] Statistical study in England suggested that physicians are in more danger of dying of poliomyelitis than other persons.[79] Previous observations elsewhere had shown that the risk of infection among hospital personnel was surprisingly low.

Intense interest persists in poliomyelitis, and yet in Florida pertussis was three times as frequent and caused more deaths.[80] In the United States in 1952, when the reported incidence was highest, there was only one case among 3000 persons of all ages and one in 1000 children.[81]

Vaccine.—In the 1956 epidemic in Chicago, 1111 cases were reported. Thirty-six victims died, giving a case fatality rate of 3.2%. Vaccination done on a large scale during the upsurge of the outbreak and afterward did not provoke any attacks. Among the reported cases, 835 victims were paralytic and, of these, 285 had received one or two injections of vaccine. Of 125,000 children given one injection, 200 had paralytic attacks; fewer attacks occurred after two injections, and none followed three injections.[82] According to Ratner, the program of vaccination in the epidemic was a failure. One-third of cases occurred in vaccinated children, and 212 were paralytic. In an epidemic in North Carolina, the incidence of paralytic cases increased despite vaccination. He made caustic comments and serious charges against the plan of manufacture, distribution, use and value of the Salk vaccine and predicted a collapse of the national program.[83]

Other reports were more optimistic. Among vaccinated English children, the incidence of paralytic disease was one-fifth as high as in those not vaccinated. These results were better than the 72% of protection reported in an American survey. The incidence of nonparalytic infection was not reduced by vaccine.[84]

Because of the wide annual fluctuations in the incidence of poliomyelitis, it is not possible to attribute the low incidence reported in 1956, as compared with 1955, to widespread but incomplete vaccination. Yet the incidence in 1957 was even lower.[85] Tabulation indicated a greater number of cases between 1948 and 1956 than in the preceding 15 years. This may be due in part to better diagnosis and registration. The over-all frequency of paralysis by age groups was similar in 1955 and 1956, but paralysis in vaccinated persons less than 20 years old was lower (34%) than among

unvaccinated ones (60%). Vaccine apparently prevented some paralytic cases. Crude estimates indicated effectiveness of about 75%. Vaccination was of less value in preventing mild and inapparent infections. Its primary purpose would be to lower the total incidence of poliomyelitis.[86] The low death rate in 1956 (0.4 per 100,000) was about the same as in 1938, 1942, and 1947, when vaccine was not used.[81] Because of incomplete clinical statistics, mortality rates approach accuracy better in regard to the long-term trend of poliomyelitis.

Vaccination had no great influence on subsequent alimentary infection. Forty household infections were detected among 300 vaccinated persons. Dead virus vaccine probably will not eliminate polio virus in the manner that vaccinia vaccine controls smallpox.[87] In chimpanzees, vaccine limited the duration and degree of intestinal infection. If this action applies to humans, it is likely to reduce the risk of exposure and result in a consequent loss of booster effects from natural infections in communities where sanitary standards are high.[88] According to Horstmann, persons whose antibody is acquired from natural inapparent infection are more resistant to subsequent infection than those vaccinated with formolized vaccine. Demonstrable antibody is only a part of the mechanism of defense.[89]

Among 3970 children who received two injections of vaccine, untoward reaction occurred in 490 (16.5%). Allergic responses affected 106, and most of these had received penicillin previously. Reactions may have been due to traces of penicillin in the syringes.[90]

Poliomyelitis-like Diseases

New technical procedures brought to light a number of viral entities formerly confused with poliomyelitis, especially in its mild and nonparalytic forms. Yet uncertainty arises at times as to the identity and etiologic significance of the newly discovered viruses. For example, in Russia, an agent isolated from patients diagnosed as having poliomyelitis was different from the three standard types of polio virus. It was named Type 4, but in tests made elsewhere it was classified as Coxsackie Type A7 virus.[91]

Study was made of families in an isolated Scottish community where poliomyelitis had never been recognized. Pleurodynia had occurred in the area. Among 294 persons, Coxsackie B3 virus was obtained from five children, and Types 2 and 3 poliomyelitis virus were found in one boy. Antibody against polioviruses Types 2 and 3 was demonstrated only in the sister of the boy and in one neighbor child.[92] As in the survey just mentioned, poliomyelitis in a single patient may not spread to others. Among 400 children in an institution, 1 child had paralytic poliomyelitis, and yet no others were infected. On the other hand, serologic evidence indicated widespread infection with Coxsackie B4 virus and ECHO Type 14 virus.[93]

Coxsackie and ECHO viruses reside as commensals in many healthy persons, and their causative relation to disease may be doubtful unless specific antibody is evoked.[94] Of importance in regard to these diseases and especially to poliomyelitis is the recognition serologically or culturally of inapparent infections. These far outnumber overt ones. Their statistical inclusion in epidemic spectrums has forced a drastic revision upward of the incidence rate and downward of the previously stated mortality rate of these and of many other infectious diseases.

Coxsackie Disease.—As mentioned previously, serologic evidence revealed widespread infection with Coxsackie virus among children in an institution, and yet none were sick.[93] On the other hand, the virus may give rise to disease of varied nature. An epidemic caused by Type 5 virus in Minnesota resembled one of poliomyelitis and affected more than 60 persons.[95] Virus of the same type probably caused acute pericarditis.[96] Coxsackie virus was present in the blood of a person five days before the onset of meningitis.[97] Other manifestations are pleurodynia, herpangina, and acute

myocarditis. Parotitis in four patients with herpangina raised the question of mumps,[98] but no mention was made of salivary gland virus or of the possibility of secondary infection with oral bacteria.

To illustrate further the etiologic uncertainties that arise, an epidemic of 52 cases in England consisted of 27 patients with meningoencephalitis, 17 with pleurodynia, and 8 with headache and vomiting. Coxsackie disease was suspected, but similar cases elsewhere at the same time were said to be of Nottingham meningitis.[99]

ECHO Viruses.—Numerous epidemics of Type 9 ECHO virus meningitis characterized by a rubellaform rash occurred in Europe and in Canada.[100] Three reports appeared in *The Lancet* of March 9, 1957, and two, in German journals.[101,102] Other observers suggested that Type 9 virus was but another member of the Coxsackie group.[103] Type 9 virus caused lesions in mice like those of Coxsackie infection.[104] The virus is chiefly neurotropic and weakly dermatotropic in contrast with measles virus.[100]

ECHO virus Type 3 caused diarrhea in 12 of 21 premature infants. They excreted the virus and developed antibody against it, neither of which occurred in the uninfected ones.[105] In other epidemics apparently caused by E. coli O127:B_8, no cytopathogenic virus was implicated.[106] If both were present, it probably would be difficult to decide if one or both or neither were pathogenic.

Filterable agents unrelated to ECHO viruses isolated from cattle were named ECBO (enteric cytopathogenic bovine orphan) viruses. Antibody against them was present in cattle but not in man or swine.[107]

Epidemic Neuromyasthenia: Benign Myalgic Encephalomyelitis.—To add to the complex problem, other epidemics of poliomyelitis-like disease without dermal eruption occurred for which no cause has been found. In sporadic cases in England, mistaken for poliomyelitis, there was paresis of one or more limbs and muscular disturbance detected by electromyography.[108] An outbreak in a hospital in Washington, D. C., affected nurses almost exclusively. Among 84 nurses, 21 had myalgia and transient paresis and 18 had minor nondescript illness.[109] A similar epidemic among 1041 persons in Florida had an attack rate of 6.3%, as revealed by a house-to-house canvas. No children were involved. The incidence among physicians and nurses was 42%. There was difficulty in differentiating victims from apprehensive persons with factitious symptoms.[110] What seemed to be a similar disease was observed in an English hospital in a four-month summer period when 292 of the personnel were sick. It was characterized by systemic involvement of the lymphoreticular and central nervous systems, intense myalgia, sore throat, and weakness. The cranial nerves often were affected; convalescence was slow, and all victims recovered.[111]

St. Louis Encephalitis

Probably the largest epidemic of St. Louis encephalitis since 1933 occurred in Texas in the summer of 1954. The estimated attack rate was 164 per 100,000. There were only 10 deaths, chiefly in victims with other chronic disease. Description of the outbreak appeared in three papers in the *Public Health Reports* issue of June, 1957.

Equine Encephalitis

When epidemic diseases recur at long intervals, their past existence may be forgotten and they are regarded as "new" ones. This occurred with pandemic influenza in 1918. Hanson resurrected reports undoubtedly of equine encephalitis in Massachusetts in 1831. Meningitis was recognized at the time.[112] Eastern equine encephalitis reappeared in epidemic form in Massachusetts but not in nearby regions in 1938, 1955, and 1956. The reported mortality rate of 68% of 50 patients almost certainly is exaggerated. Inapparent and mild attacks were not included statistically. Survivors less than 10 years old had more and graver sequels than older ones, in the form of mental

retardation, emotional instability, convulsions, and paralyses.[113]

A variety of neurologic disturbances may characterize cat-scratch disease. Encephalopathy, radiculitis, and myelitis are transient sequels.[114]

Rabies

Although antirabic vaccines have been used for 70 years, their immunizing value still is doubtful. In experimental studies, antirabic serum was superior to vaccine and the use of both gave the best protection. A single dose of antiserum should first be given intramuscularly, much of it around and under the site of the wound, followed by the usual course of vaccination. A table conveniently outlining the procedure appeared in Habel's paper.[115]

In a field trial among 29 persons bitten by a rabid wolf in Iran, 5 severely exposed persons apparently were protected by the prompt injection of antiserum and vaccine. Three of five who received vaccine alone died. Measurements showed antibody in the serum early and late after combined injections but only in the late stage after vaccine alone.[116]

In South Carolina, in 1955, forty per cent of persons exposed or supposedly exposed to infection were unnecessarily vaccinated. In the past five years, five persons died of rabies and three died of vaccinal encephalitis.[117] Virus is present in the saliva of infected persons. Attendants who treat patients are in danger of infection if they are bitten or scratched. Should this happen, prophylactic measures are indicated. Unauthenticated instances of man-to-man transmission have been reported.[118]

Rabies is disseminated among bats in Florida. Among thousands studied, rabies affected 0.2% of colonial bats and 1.5% of free-living ones. In one study, 5 of 35 bats tested because of some abnormality were infected. Twelve of these had bitten people. The absence of Negri bodies in 50% of infected bats impedes diagnosis.[119]

Measles

Tyler reviewed knowledge of the neurologic involvements during measles. Diffuse encephalitis, arterial infarction, acute cerebral edema, vascular and neuronal changes, and retrobulbar neuritis may occur. The prognosis is bad in infants, who usually have sequels.[120]

Enders reviewed the development of technical procedures which led to the isolation and cultivation of measles virus. The way seems clear for the preparation of a vaccine. Methods also are promised to detect inapparent infection and the occurrence of second attacks and to determine the nature of measles encephalitis.[121] The virus caused the formation of multinuclear giant cells, inclusion bodies, and fusiform or stellate epithelial cells in cultures of human amnion cells.[122]

Rubella

Early report of the risk of stillbirths or congenital malformations in 50% of cases of maternal rubella in early pregnancy was exaggerated. The danger is not so great. In a series of 104 women who had rubella in the first trimester of pregnancy, the incidence of deformed offspring was 9.7%. Therapeutic abortion therefore must be seriously considered before it is recommended. Girls and young women should be exposed to rubella before marriage.[123]

Varicella

In a six-month period, 148 patients with varicella were studied. Of 30 adults, 10 had pneumonia, but none of 118 children did. The pneumonia resembles other viral ones clinically and pathologically.[124]

Mumps

Mumps virus can be grown in tissue cultures sown with specimens of spinal fluid, urine, and saliva from patients as early as the second day of disease.[125] A rising titer of the complement-fixation test occurred in a number of cases of subacute thyroiditis in

Israel. An agent identical with mumps virus was isolated from two of the patients.[126]

Hepatitis

Clinical and laboratory evidence of hepatitis appeared in 4% of 144 persons who had been given injections of blood. Three donors whose blood had caused hepatitis in recipients had no signs of hepatic disturbance. Blood from 33 other donors whose bilirubin was abnormally increased in amount did not cause hepatitis. Obviously there is no way of selecting safe donors. The most effective way to reduce the incidence of serum hepatitis is to discontinue unnecessary transfusions.[127]

The prognosis was good in 12 patients who had retention of bile lasting five weeks to six years. Corticotropin administered for four days caused a diminution of bilirubin in the serum and a sense of well-being but had no influence on the hepatic lesion. It was called a convenient whitewash.[128] Cortisone should not be used in treatment except for the severest attacks. It may shorten the course of disease when the serum bilirubin is greater than 15 mg. %; when anorexia, nausea, and vomiting cannot be controlled otherwise, and in the presence of hepatic necrosis, fetor hepaticus, or coma.[129] Administration of chlortetracycline orally in patients with hepatic coma is said to reduce the amount of ammonia in the blood by suppressing bacterial action in the intestine.

Aspiration-biopsy specimens from 126 patients contained cytoplasmic inclusions and Councilman hyaline bodies. Centrolobular parenchymal necrosis was seen in 32% of sections, the majority of which came from patients with serum hepatitis. Necrosis may lead to irreparable damage.[130] Leukopenia occurs at times during hepatitis, and a rare fatal case of agranulocytosis was observed. It was caused either by the virus or by staphylococci present in sections of the liver.[131]

Infectious Mononucleosis

More than 20 instances of rupture of the spleen during infectious mononucleosis are on record. Another spontaneous one was observed.[132]

Viral Dysentery

Most of the views I advanced in 1945 in regard to viral dysentery were substantiated in four papers in the November, 1956, *American Journal of Hygiene*. The term viral dysentery was avoided in spite of its fitness. The incidence of the disease among families in Cleveland was second only to that of minor respiratory tract infections. As in my report, the association of symptoms of nasopharyngitis with intestinal disturbance occurred often enough to warrant an etiologic connection. On the other hand, six outbreaks of epidemic vomiting observed in English schools and families were not accompanied by respiratory or intestinal symptoms. The incubation period appeared to last 24 to 72 hours.[133]

Japanese investigators regularly isolated an ECHO-like virus called the Niigata strain from the stools of volunteers infected with the virus obtained from patients with viral dysentery. The relationship of the virus to the disease was doubtful. It may have been a commensal.[134]

Herpes Zoster

A study of 206 patients with herpes zoster provided knowledge of the natural history of the disease and a standard by which therapy may be evaluated. Thirty-two patients were less than 20 years old, and in most of these the disease rarely lasted more than 14 days. It was severer and more persistent in older patients, often with ocular involvement. Neural disturbances and pain occurred in 66%, and a systemic reaction affected 6%, especially young victims. Lesions lasted longer than 55 days in four patients and a year in two. The dorsal nerves were involved in 55% of cases, and the divisions of the fifth cranial nerve, in 17%. Neuralgia persisted in 20 patients.[135] Similar findings were noted in 916 other patients. Neuralgia occurred in 17% of victims less than 20 years old and in 91%

of those more than 70. Generalized disease evolved in 1%, and 4% had some form of lymphoma in addition. Therapy including rhizotomy was ineffective.[136]

It has become clear that many viruses regarded as dermatotropic (herpes simplex, varicella, rubella), neurotropic (Coxsackie), and glandulotropic (mumps) and others (infectious mononucleosis) affect different tissues and organs as well and may cause systemic disease. Cardiac, gastrointestinal, renal, and respiratory tract disturbances in addition to cutaneous lesions occurred during herpes zoster.[137]

Hemorrhagic Fever

Hemorrhagic fever observed in Korea during the war is not confined to that region. Russian physicians studied a similar disease in Astrakhan. It probably occurs throughout the southern Soviet Union.[138]

A virus was isolated from a patient with Behcet's disease, and neutralizing antibody against it was demonstrated in titer of 1:128 in 3 of 11 patients. The virus grew in eggs but not in ordinary tissue culture and was not virulent in mice, guinea pigs, or rabbits. The disease in man usually is benign unless the nervous system is involved, when the death rate is 50%.[139] Cuffing of cerebral blood vessels with lymphocytes is further evidence in favor of a virus as the cause.[140]

Other Studies

Sprunt reviewed knowledge gleaned from 152 articles on the newly discovered viruses and viral diseases. Rare infections like viral myocarditis and giant-cell pneumonia are covered,[141] but no mention was made of viral dysentery, at times one of the most widespread of epidemic diseases. Newly recognized viral infections of the nervous system were discussed editorially.[142] The English editor may be twitted for using the noun "virus" instead of viral as an adjective. In the past few years, more than 65 "new" viruses have been isolated from man in addition to the 60 dealt with in current textbooks. Many of them are as yet unassociated with disease and may represent the normal viral flora of the body or of cells. Knowledge of the intracellular residence of viruses may lead to further discoveries about diseases whose cause still is unknown[143] and of a number of "orphan" viruses.

In regard to viruses as oncogenic agents, Burnet feels that these represent only one of the means by which mutations from normal to malignant cells may be induced. Probably any virus that can find a cell either normal or one or more stages on the way to uncontrolled growth in which it can cause proliferative changes may have some or all the qualities of a cancer virus. All viruses may have some ability to provoke proliferation, but such changes are caused by other factors as well. Any claim that all cancers are of viral origin is unjustified. "A final solution will probably never be possible."[144]

In a manner akin to the artificial transformation of one type of pneumococcus into another, greater changes have been induced in viruses. Three fractions of ribonucleic acid recombined with the protein of tobacco mosaic virus gave rise to three reconstituted viruses able to cause widely different changes in plants into which they were inoculated. Perhaps other new viruses can be synthesized now that poliomyelitis and Coxsackie viruses have been crystallized. Variant forms may be "made to order" for the preparation of suitable vaccines.[145]

Cytopathogenic changes were evoked in renal-cell tissue cultures by Eastern, Western, and Venezuelean equine; St. Louis, Japanese B, and Murray Valley encephalitis viruses, and Ilheus and West Nile viruses. Tissue culture procedures are equally or more reliable for diagnosis than the inoculation into mice.[146] Human bronchial mucosa grown in cultures was resistant to the cytopathogenic effects of poliomyelitis virus and adenovirus that cause destruction of renal and HeLa cells. Perhaps the mucosa of the respiratory tract serves as a protective factor against infection.[147] On the other hand, the viruses just mentioned and a number of others caused cytopathogenic ef-

fects in cultures of human tonsillar epithelium. Influenza viruses did not cause clear-cut changes.[148]

Bacillary Diseases

Tuberculosis

In the United States at present about 60,000,000 persons are infected with tubercle bacilli. Of these, 1,000,000 have some signs or symptoms of disease and about 350,000 have active tuberculosis.[149] Persons with minimal or inapparent infection may serve as spreaders of the disease. Primary tuberculosis in children usually is clinically inapparent but can be detected by the tuberculin test. Therapy with isoniazid and aminosalicylic acid does not eliminate the bacilli but is said to minimize the danger of progression and of serious disease.[150]

After the enforcement of rigid precautionary measures in the University of Minnesota Hospital after 1930, the morbidity rate declined greatly. Medical students no longer die of tuberculosis. Between 1919 and 1932, ninety-two had lesions and eleven died; in the past 14 years, only one had a pulmonary lesion large enough to cast a shadow.[151] Studies in England, like earlier ones in Minneapolis, showed the incidence of tuberculosis among persons of low social status in "flophouses" to be far greater than in the general population. Among 1200 men examined roentgenographically, 68 were tuberculous, an incidence of 56 per 1000. In one house, 8 of 47 were infected.[152] In another group of indigent wayfarers, 5% of 583 were tuberculous.[153] The incidence of tuberculosis also is higher among laboratory and mortuary workers.[154] In one hospital laboratory, three technicians originally tuberculin-negative acquired dermal tuberculosis of the finger from handling cultures.[155]

The possibility of tuberculous dogs and cats serving as sources of infection in man was considered. Nine persons in contact with infected dogs were found to have tuberculosis. Among pets owned by patients with active disease, tubercle bacilli were present in the intestine of two dogs and two cats.[156]

In a Canadian village of 2300 persons, 40 cases were discovered in two years, an incidence of 5.5 per 100, as compared with 1.7 per 100 in the Province. Nineteen victims had chronic pulmonary tuberculosis, twelve were acutely ill, and others had pleural, meningeal, skeletal, or miliary involvement. The incidence of tuberculin reactors in the village was 44%, and it was less than 10% in the Province. It was predicted that small epidemics will be more frequent in the future, owing to the diminution of the number of immune or partly immune persons who react to the tuberculin test.[157]

Miliary calcifications in the lungs of healthy persons once were thought to represent evidence of recovery from tuberculosis. Most or perhaps all of such healed lesions now are ascribed to histoplasmosis. Miliary tuberculosis probably was a fatal disease until the advent of antimicrobic therapy. Two patients were observed who recovered after therapy, but they had a recurrence of pulmonary miliary tuberculosis 18 and 27 months later.[158]

Over a three-year period in a hospital for tuberculosis, 18% of inmates were found to have pulmonary fibrosis, pneumonia, bronchiectasis, histoplasmosis, coccidioidomycosis, pleurisy, neoplasm, sarcoidosis, granulomas, or abscess of other origin, in that order of frequency.[159] A similar array of diagnoses was made in 16% of 5324 patients originally thought to have tuberculosis and admitted to an Army Hospital. Evidence of pulmonary disease was absent in 11%, a reflection of poor diagnostic acumen.[160] In a Naval Hospital, 26% of 507 patients originally diagnosed as having tuberculosis had other disease.[161]

Study was made of the accuracy of tests for the diagnosis of tuberculosis. Active tuberculosis is a clinical, not a pathologic, diagnosis and is substantiated by the demonstration of tubercle bacilli in or from the lesion. The accuracy of properly performed tuberculin skin tests established the pro-

cedure as the keystone of diagnosis. A positive reaction in a child less than 6 years old indicates active primary infection. The sedimentation rate of red cells is of no diagnostic value, but a single positive bacteriologic specimen is sufficient to warrant therapy. Material obtained at biopsy is of chief value in the diagnosis of extrapulmonary lesions.[162]

A symposium on rare manifestations of tuberculosis appeared in the July 24, 1957, issue of *Proceedings of the Staff Meetings of the Mayo Clinic*. Miliary tuberculosis of the liver, before extrahepatic spread occurs, is a rare condition. Twelve cases were observed in which diagnosis was made by needle biopsy. Treatment with isoniazid and aminosalicylic acid was successful in eight patients.[163] Tuberculous axillary adenitis occurred in a patient with minimal inactive tuberculosis after application of a skin test with purified protein derivative to the arm.[164]

Therapy.—The traditional long period of enforced bed rest has been shortened after surgical operations, viral hepatitis, rheumatic fever, and febrile disease in children. In two studies of patients with moderately advanced or far-advanced tuberculosis, detailed observations also revealed no detectable differences in the course of the disease and the speed of recovery in relation to rest or activity. Prolonged rest in bed generally was not needed, provided adequate specific therapy was applied.[165] The morale was better in ambulatory patients.[166]

In a Canadian survey, 11% of 686 cultures of Mycobacterium tuberculosis obtained from patients before therapy resisted streptomycin, 41% resisted isoniazid, and 16% resisted viomycin.[167] In another community, 125 of 2400 tuberculous patients excreted drug-resistant bacilli. Bacilli primarily resistant to antimicrobics were present in 15. The matter is developing into a problem of public health.[168]

In one large hospital before 1948, all victims of tuberculous meningitis died. After streptomycin and aminosalicylic acid were used, the mortality rate fell to 84%, and after therapy with isoniazid, to 54%. There was no need for intrathecal therapy.[167] No mention was made of sequels among the 18 patients who recovered.

From 15% to 20% of treated tuberculous patients deteriorate, do not improve, or have a relapse. The chief causes of failure are inadequate supervision of patients not in hospitals, unusual susceptibility to tuberculosis, inadequate rest, refusal to take treatment, drug-sensitivity, resistance of bacilli to antimicrobics, and errors in diagnosis.[170]

A committee discussed the use of adjuvant steroid therapy and found agreement only on its value in tuberculosis meningitis. There are no clearly formulated indications for hormone therapy in other forms of tuberculosis. It may be of help in fulminating or disseminated disease which shows little or no response to standard antimicrobial therapy. Hormones should not be used unless the bacilli are susceptible to antimicrobics.[171]

BCG Vaccine.—Controversy about the value of BCG vaccine continues. In spite of objections by several authorities, a Medical Advisory Committee urged its use. It was said that interference with the reaction to the tuberculin test as a diagnostic aid will be compensated for by a reduction in the incidence of tuberculosis after vaccination.[172] There is agreement, however, that vaccination is desired for infants and children in areas of high incidence, for persons unavoidably exposed to infection, and for family members exposed in tuberculous households.[173] Wallgren, a former advocate of vaccination, predicted an end to it if chemoprophylaxis proves to be satisfactory. Vaccination of all persons who do not react to tuberculin is unnecessary.[174] Pollock recommended vaccination of English children at age 10, but mass inoculation of unexposed infants is unjustified.[175] According to James, vaccination with BCG will revert ultimately to its former obscurity. He protests against the waste of "energy and resources of a pseudoscientific ritual."[176]

The case against the use of BCG vaccine was presented forcefully by Myers. The last of 17 cogent conclusions stated, "Mass BCG campaigns not only give recipients an unjustified sense of security but deprive well-established fundamental methods of funds, as well as time and effort to workers." None of the numerous vaccines tried has passed the controversial stage.[177]

About one-half of 1533 infants less than 6 months old in an area of high incidence of tuberculosis in Virginia were vaccinated; the other half served as a control group. Although 16% of the control group got tuberculosis as revealed by the tuberculin test, only three had overt disease. All of the vaccinated ones escaped clinical disease.[178] Kendig felt that the value of the procedure was not demonstrated conclusively. Over a five-year period, 256 nurses were tuberculin tested. Of these, 64% did not react, and most of these then were vaccinated. The incidence of tuberculosis later was 3.6% in both vaccinated and unvaccinated ones. There was no evidence that vaccine gave a significant degree of protection or altered the subsequent course of tuberculosis.[178a]

Experimental Studies.—Heat-killed tubercle bacilli were injected intradermally into sensitized guinea pigs. One group then was treated with cortisone. In these the bacilli disappeared as rapidly as in the control animals but without the participation of mononuclear or epithelioid cells, which were suppressed by the hormone. Evidently cortisone did not inhibit the disposal of the bacilli by some humoral mechanism.[179] One wonders what the behavior of live bacilli would be under similar circumstances.

Chromogenic Acid-Fast Bacilli.—The significance of pigment-forming acid-fast bacilli found during tuberculosis or supposed tuberculosis is unknown. "Yellow" bacilli were present in the purulent lymph nodes of 10 children, but the disease was mild, and healing took place.[180] Two strains inoculated in large numbers caused mild disease in monkeys.[181] Three other strains repeatedly isolated from patients failed to affect monkeys. Their probable origin as a result of dissociation induced by antimicrobic therapy was considered, but similar variant forms have not appeared during cultural studies. The three strains were the only ones encountered in a year in a sanitorium.[182] In another study over a five-year period, atypical acid-fast bacilli were found in 65 of 69 patients with pulmonary disease. Antimicrobic therapy seldom was effective in eliminating them from the sputum. Pathologic changes in pulmonary tissue resected from seven patients were those of tuberculosis. The bacilli were classified as nonphotochromogens.[183]

Tuberculosis and Sarcoidosis

Advances in the knowledge of sarcoidosis, controversy as to its relationship to tuberculosis, and the value of the Nickerson-Kveim test were reviewed.[184] A case of cryptococcosis with sarcoidosis was described.[185] No mention was made of a possible relationship between sarcoidosis and histoplasmosis or other fungal diseases which at times accompany or cause the clinical and pathologic picture of sarcoidosis. Sarcoidosis occurred in identical twins, one of whom had cryptococcosis.[186]

Sixteen periods of pregnancy were observed in 10 women who had sarcoidosis. In eight the disease seemed to be ameliorated during gestation. Three fetal abnormalities resulted. Since pregnancy often increases the severity of tuberculosis, the observations offer further support to the view that tuberculosis and sarcoid disease are unrelated entities.[187]

Salmonellosis

In a 16-year period, salmonellas other than Salmonella typhi were cultivated from 2625 of 144,500 specimens, especially from stools, in Massachusetts. Of the 50 types identified, 99% belonged to Groups A, B, C, D, and E. Group B (S. typhimurium) predominated. The incidence was highest in August, lowest in February, and greatest among young children. Clinically, gastroen-

teritis accounted for 70% of the resulting illnesses and the typhoidal or focal septic behavior for about 6%, the latter especially from S. choleraesuis. The mortality rate was 1.4%. Aside from better diagnosis, salmonellosis was thought to have increased in incidence. Restraint was recommended in the use of antimicrobic therapy for gastroenteritis. When Salmonella infection is restricted to the gastrointestinal tract, it "is more than questionable whether antibiotics have any place at all" because of the danger of superinfection with other germs. The incidence of typhoid has decreased since 1940; Type A bacilli predominated in the patients observed, and the death rate was 8%.[188]

The importance of determining the types of salmonellas was emphasized for clinical, epidemiologic, and statistical reasons. The antityphoid vaccine in current use affords protection against only the rare infections caused by S. typhi, and S. paratyphi A, B, and D but not against others which are more dangerous and account for nearly half of the cases of salmonelloses in the United States.[189] Salmonellosis occurs during sickle-cell anemia, as it does in hepatitis, in debilitation, and after gastrointestinal surgery, and for the same reason, namely, interference with natural resistance. Three instances of Salmonella osteomyelitis and one of bacteremia were noted among 36 cases of sickle-cell anemia.[190] An unusual source of infection with S. paratyphi B was a sick turtle from which five children contracted acute enteritis.[191]

Typhoid

Relapse occurs as often in typhoid patients adequately treated with chloramphenicol as in untreated ones. The rate was even higher in those who received insufficient amounts of the drug. Relapse occured in spite of a high titer of antibody in the blood. As the cause, Watson blamed the persistence of bacilli intracellularly in the reticuloendothelial system and reinvasion when the amount of the antimicrobic was too low or absent.[192]

Among prisoners of war in Korea 203 intestinal perforations were recorded in victims of paratyphoid.[193] Although the incidence of the disease was not stated, the number seems high in contrast with the generally reported low percentage of perforation. In my series of 105 cases in Indonesia, perforation occurred but once.[194] An epidemic of paratyphoid B involved 279 persons in Pennsylvania. Milk contaminated by a carrier in a dairy was the vehicle of infection. Chloramphenicol, it was said, had no beneficial effect on the acute stage of the disease in 59 patients.[195] Most other observers found that therapy shortens the duration of disease.

Although antityphoid vaccines have been used for about 50 years, no controlled field study acceptable by modern standards to test their value has ever been made. In Yugoslavia, where careful test was made on 35,000 people, the case rate per 1000 of typhoid of persons vaccinated with phenolized vaccine was 2.3%, as compared with 8.9% in the unvaccinated ones. Alcohol-treated vaccine was less effective. The Vi antigen did not seem to play an important role in protection.[196] Similarly controlled field studies would be desirable for the appraisal of vaccines against smallpox, typhus, yellow fever, and cholera.

Brucellosis

Spink's observations cast light on the importance of specific hypersensitivity to Brucella. Two persons who had not had brucellosis were infected accidentally with relatively avirulent Strain 19, used as a vaccine for livestock. A latent period elapsed before symptoms appeared. Two others who had had brucellosis previously became sick a few hours after reinfection, probably as a result of having been sensitized. Strain 19 Brucella should not be used for the immunization of humans.[197]

Unless brucellosis is kept in mind, diagnosis often is missed. A number of children in England regarded as having influenza, migraine, sarcoidosis, tuberculosis, spinal

radiculitis, and psychic disturbance were found to have brucellosis. Treatment with streptomycin and chlortetracycline usually was successful, but relapse occurred.[198] A description of the disease as it occurred in 228 patients in Egypt was published.[199]

Tetanus

The April 3, 1957, *Proceedings of the Staff Meetings of the Mayo Clinic* contained the report of a symposium on tetanus. The logical view of Abel in regard to the transportation of toxin by way of the blood stream has been challenged. British investigators renew the idea that toxin spreads along nerves from the site of infection to the central nervous system. If this be the case, tetanus toxin is unique. Ninety-one cases were reviewed. Of these, 56% recovered. About 76% of victims in the second decade of life survived, as compared with 44% of those more than 50 years old. Tetanus occurred in five persons who had received prophylactic measures. Although the mortality rate has not been lessened by antitoxic serum, improvements in general management have reduced the death rate from 57% before 1934 to 27% after 1945. Detailed directions for immunization were outlined.

Brazilian physicians reported a death rate of 23.7% among 1047 treated patients.[200] Generalized tetanus was studied in 202 Puerto Rican patients. Several second attacks were recorded. The usual dose of antitoxin did not always prevent the disease. Penicillin was used at times but had little influence on the death rate, which was about 35%.[201]

Clostridium welchii may cause food poisoning. Volunteers who ingested cultures of one strain had colic and diarrhea 12 hours later. Another strain gave similar results, but a third one was innocuous. No rise in circulating antibody was detected.[202]

Diphtheria

With an annual total of about 2000 reported cases and a fatality rate of 6% to 7%, diphtheria is of more importance to public health than brucellosis, psittacosis, typhoid, or typhus. Localized outbreaks continue to occur.[203] In the autumn of 1954, there were 141 cases and 4 deaths in Detroit. Restrained instructive publicity in the press avoided panic and led to the administration of toxoid to 80,000 children.[204] Another outbreak occurred in Philadelphia. Ambulatory victims with unrecognized mild disease and nondescript pharyngitis far outnumber those with so-called typical attacks. They serve as dangerous spreaders of infection and may themselves have postdiphtheritic paralysis.

Other Bacillary Diseases

Report of 11 cases of meningitis caused by Klebsiella pneumoniae was added to the 140 previously described. Of 61 untreated patients, 57 died. Among 41 patients treated with various antimicrobials, 40 recovered. Meningitis usually accompanied pulmonary infection in debilitated patients and most often was caused by bacilli of Types 1 and 2. Sulfonamide compounds in combination with other antimicrobials at present seem to be the drugs of choice for therapy.[205]

In a small party of Eskimos poisoned by eating decomposed seal meat only one man survived botulism. At necropsy, petechial hemorrhages in the gastric mucosa and multiple thromboses of the meningeal vessels were found.[206]

Tularemia caused pericarditis in one patient,[207] and in 4 others with pharyngitis, diphtheria was wrongly suspected.[208] Empyema in a man 77 years of age was caused by Pasteurella multocida, a bacillus associated with cat-bite fever. It is possible that the germ resides at times as a commensal in the respiratory tract and may become invasive when resistance is reduced.[209]

Septicemia with Pseudomonas aeruginosa (Bacillus pyocyaneus) occurred in 29 of 172 Peruvian children with severe burns. The appearance of dermal nodules had a bad prognostic import. No form of therapy was effective.[210] Only three cases of melioidosis,

a glanders-like infection, have been reported on from the United States. A patient with melioidosis of 10 years' duration was observed, and data on 17 others were presented.[211] The infection is imported from endemic centers in the Far East.

Sir Leonard Rogers reviewed 30 years of research on the control of cholera. In his opinion, vaccination reduced the incidence of infection in pilgrims to Mecca.[212] It is likely that increased knowledge and improved sanitation also played a role. Many observers are less optimistic about the effectiveness of anticholera vaccines.

Coccal Diseases

Staphylococcosis.—In spite of the opinion of some authorities to the contrary, the present interest in staphylococcal infections has been induced by the increased incidence of staphylococci resistant to increasing numbers of antimicrobics and the consequent failure of therapy. It now is largely a hospital problem, but with continued indiscriminate use of antimicrobics by practitioners the problem of resistant cocci will inevitably extend to the population at large. This is foreseen where economic or political conditions permit the lavish and wasteful use of expensive drugs, even when these are relatively or entirely unnecessary.[213]

In an English hospital, staphylococcal diarrhea became a major cause of death after partial gastrectomy and in chronic respiratory tract infections when patients had had antimicrobic therapy. Two epidemics involved the surgical wards. In a two-year period, 31 instances of diarrhea followed antimicrobic therapy. Staphylococci, mostly antimicrobic-resistant, were cultivated from 20 patients. Fourteen died, including seven who had had partial gastrectomy. The most important measures to correct matters are restriction of antimicrobic prophylaxis and therapy and reduction of the numbers of staphylococci in the environment.[214] In a nine-week period in another hospital, 31 of 83 patients in a surgical ward acquired staphylococcal infection from an undetected source. The cocci belonged to one type and resisted penicillin and streptomycin. After chloramphenicol and erythromycin came into use, resistance against these drugs also developed.[215] According to McDonald, six persons had severe infection and two died after surgical operations by a surgeon with a furuncle on his arm. Covering the lesion failed to prevent infection of the patients.[216]

In a survey of 100 staphylococcal infections acquired in a hospital, many were serious or fatal. They were associated with debilitated patients or followed intravenous therapy and catheterization. Only 3% of the cocci were sensitive to all antimicrobics tested, and 26% were sensitive only to bacitracin. If the same rate of "hospital infection" were maintained for a year, 450 infections and 76 deaths were predictable. On the other hand, 30% of patients contracted staphylococcal infections before entering the hospital, and these seldom were severe. Forty per cent of the cocci were sensitive to the antimicrobics tested, and only 35% resisted penicillin.[217] Without the use of antimicrobics, Adams controlled the alarming increase of infections in surgical wards by the proper preparation of hands and operative sites and by reduction of airborne and contact infection.[218]

According to Turnbull, the relationship of micrococcic enteritis and pseudomembranous colitis is not clear. He observed five cases of enteritis after surgical operation, in four of which antimicrobics had been used beforehand. Staphylococci caused fulminating infection elsewhere in the body in one patient, but none were found in the inflamed intestine, as if a toxic effect were accountable.[219] Staphylococci present in the intestine during enterocolitis may or may not be the cause.[220]

About 33% of patients not in hospitals were persistent nasal carriers of staphylococci, of which only 16% resisted penicillin. About 5% of carriers had had one or more staphylococcal lesions annually, and only a few needed therapy with penicillin. A cream containing neomycin and bis-*p*-

phenyldiguanidohexane applied intranasally suppressed staphylococci and decreased the number of infections.[221]

Serious epidemics occurred in hospital nurseries and caused pyoderma in infants, mastititis and abscesses in mothers, and a number of deaths. After improvement in aseptic technique and cessation of new admissions, but without the use of antimicrobics, the outbreak stopped abruptly.[222] Staphylococci of one strain infected 46% of 117 newborn infants in a hospital. Infants with inapparent infections disseminated large numbers of cocci. Among 23 mothers who nursed carrier infants, 39% were infected.[223]

Some physicians agree with McDermott's view and find no convincing evidence to prove a shift for the worse of the crude equilibrium between man and Staphylococcus. Over 16 years, 109 cases of staphylococcal bacteremia were observed in a hospital. It was associated chiefly with carbuncles, furuncles, cellulitis, pyelonephritis, and lymphomas and often followed operations on the prostate gland. Thirty-seven patients died.[224]

Staphylococcal Endocarditis.—Cure was reported in six of seven patients with staphylococcal endocarditis after the administration of huge doses of penicillin combined with oxytetracycline and streptomycin. An initial dose of 50,000,000 units (30,000 mg.) of penicillin was followed by 1,000,000 units (600 mg.) every six hours. Erythromycin, streptomycin, and probenecid in addition were recommended.[225] One wonders if enormous dosage is needed or safe, considering possible adverse effects and the zone phenomenon. Combinations of antimicrobics seldom are necessary, but for staphylococcal endocarditis they may be needed.[226]

Therapy: Penicillin still is the drug of choice if staphylococci are sensitive to it, but relatively large amounts are needed. Curiously, however, there is a zone phenomenon, or paradoxic effect. In vitro, an excessive quantity of penicillin may be less bactericidal than smaller amounts. This behavior may have importance in the treatment of infections.[227]

Neomycin and bacitracin had a satisfactory bactericidal effect, and despite their toxicity they may play an increasingly important role in therapy. Novobiocin was bacteriostatic and was bactericidal if large amounts were used. Oleandomycin was not as effective as novobiocin. In vitro tests of sensitivity of bacteria to antimicrobics serve only as a guide to the selection of the appropriate drug; clinical trial provides the answer.[228]

Garrod observed encouraging evidence of cooperation by English practitioners in restricting the use of erythromycin solely to the treatment of staphylococcal infections. As a result, it is unlikely that staphylococci at large will become resistant to the drug. Cross resistance against erythromycin, oleandomycin, carbomycin, and spiramycin may develop in vitro but may not be demonstrable in strains isolated from patients. The matter is very complex.[229] Severe criticism was made of the unwise use of combinations of erythromycin, oleandomycin, spiramycin, and tetracycline in the treatment of staphylococcal infections. There is no evidence that synergism occurs. Oleandomycin and spiramycin gave rise to resistant cocci which also resisted erythromycin.[230]

The ability of staphylococci and other bacteria to produce antimicrobic substances was known for a decade. An antimicrobic derived from staphylococci controlled experimental infection with Clostridium septicum.[231]

Thirty-years ago dissociants, or culture-phase variants, of pneumococci, hemolytic streptococci, and other bacteria known as mucoid (M), smooth (S) and rough (R) were recognized. Similar phases had not been described for Staphylococcus, which now is the most important coccal cause of death. By aging cultures of a strain of Staphylococcus aureus for many months, I educed M, S, and R forms. The aureus, or parent, form also gave rise to a white and

a buff-colored variant, each of which had similar culture phases. Spontaneous transformation of one variant into another was observed.[232]

Streptococcosis.—In contrast with its former behavior, scarlet fever is now a relatively mild disease. A few severe attacks occurred among 609 cases. Intramuscular injection of penicillin eradicated hemolytic streptococci from the throat and shortened the duration of disease. No patient had subsequent nephritis or rheumatic fever.[233]

An intramuscular injection of 300,000 units (180 mg.) of benzathine penicillin administered to 740 men reduced the carrier rate of streptococci and partly controlled an epidemic. After that dosage, the first infections appeared eight days later. Doses of 1,200,000 units (720 mg.) afforded protection for six weeks.[234] In trials elsewhere, untoward reactions to benzathine penicillin occurred in 6% of persons but without fatality.[235]

Measurements of precipitin, hemagglutination, bacteriostasis, and mouse-protection tests were unsatisfactory in the study of streptococcal infections because of nonspecific reactions and difficulties in technique and interpretation of results. With a new test, type-specific antibody was demonstrated in most patients. The reaction developed slowly and varied with the type of Streptococcus. The formation of antibody was inhibited by therapy with penicillin or chlortetracycline.[236]

Fever in the presence of cardiac valvular disease often poses difficult diagnostic and therapeutic problems. In a study of 25 patients, the most frequent cause of fever was rheumatic disease. Others were the postcommissurotomy syndrome, endocarditis, drug fever, and embolism. Lupus erythematosus, "hemoglobin pneumonia" from bleeding in the lungs, and cardiac tumor are rare causes.[237] Twenty cases of endocarditis followed surgical operation on cardiac valves among 2263 patients. Staphylococci were the cause in 14 patients, and nonhemolytic streptococci, in the rest. Eight recovered after therapy.[238]

Six patients with subacute bacterial endocarditis were treated successfully with 12,000,000 units (7200 mg.) of penicillin V, streptomycin, and dihydrostreptomycin given orally daily for four weeks. Large amounts of penicillin may cause nausea and vomiting. Streptomycin caused vestibular injury in three patients. Oral treatment is unreliable unless adequate amounts of antimicrobics enter the blood. Parenteral injection is preferable.[239] Current concepts and methods of treatment of bacterial endocarditis were summarized.[240]

Strains of Group D streptococci (enterocci) were relatively sensitive to penicillin. Their resistance to it has not increased in the past few years. On the other hand, the incidence of strains resistant to tetracyclines and to streptomycin has increased, not only of those obtained from patients treated with these drugs but from others also. All strains resisted polymixin.[241]

Rheumatic Fever.—Doubt was expressed that as high as 3% of victims of hemolytic streptococcal sore throat acquire rheumatic fever.[242] In spite of much evidence to the contrary, Wallgren questioned the role of streptococci as a cause of rheumatic fever. The disease has diminished greatly in incidence in 35 years, while streptococcal infections have not. He deems it inadvisable to administer penicillin as a prophylactic over a lifetime but would rather treat streptococcal infections as they arise.[243]

The American Heart Association recommends monthly intramuscular injections of 1,200,000 units (720 mg.) of benzathine penicillin G to prevent streptococcal infections in persons who have had rheumatic fever. If penicillin is given orally, the dosage should be 200,000 units (120 mg.) to 250,000 units (150 mg.) twice daily. Oral therapy is unreliable and may not be faithfully carried out. In either case therapy must be continuous.[244,245] Subacute bacterial endocarditis caused by penicillin-resistant viridans streptococci appeared in a person while penicillin was administered orally to prevent a recurrence of rheumatic fever.[246]

The matter of the cortisone versus salicylate drugs in the treatment of rheumatic fever is unsettled. Illingworth found cortisone to be superior, and cortisone combined with salicylates in large amounts is preferable in therapy. Because the action of the two drugs is different, both should be used.[247]

As in the case of a number of diseases, it is questionable if prolonged rest in bed is desirable for patients convalescent from rheumatic fever. A controlled study of the matter like the ones made for tuberculosis and viral hepatitis is needed.[248]

Pneumococcosis.—Acetylsalicylic acid or cortisone given with penicillin to patients with pneumococcal pneumonia gave a sense of more rapid improvement, well-being and appetite, less cough and pleural pain than in patients treated with penicillin alone. However, the rate at which both groups became symptom-free was the same. Recurrence of fever in four cases was attributed to a reaction to penicillin. Only 2 of 67 patients died.[249]

Evidently some other old-fashioned remedies also stand the test of time against an array of expensive new synthetic drugs. In a discussion of the modern treatment of pneumonias, chloral hydrate and paraldehyde were recommended as sedatives.[250] Fortunately, pneumococci have not become resistant to any antimicrobics. Penicillin remains the drug of choice.[251]

Penicillin therapy may reduce the death rate of aortic valvular disease in syphilis and rheumatic fever but seems to be less effective when pneumococci are involved. Eight cases were described in which penicillin controlled pneumococcal septicemia and endocarditis, but rupture of the valves or cardiac failure caused death 1 to 565 days after the detection of aortic insufficiency.[252] Two patients with neoplasm of the common bile duct had pneumococcal cholangiitis and septicemia.[253] This is a rare localization for the pneumococcus but not because it is soluble in bile. Bile is not lytic when serum is present.

Gonococci.—English consensus opposes oral therapy for gonorrhea. Parenteral injection of penicillin is advised, but even then cure is uncertain; relapse and reinfection may occur.[254] Other physicians recommend dosage of 600,000 units (360 mg.) of penicillin with probenecid given orally in divided doses during 24 hours.[255] One wonders if probenecid is needed. Penicillin did not kill gonococci contained in phagocytes.[256]

Mycotic Infections

Histoplasmosis.—Although histoplasmosis had been discovered in Panama in 1905, only a few cases were recognized there for four decades. Since 42% of the native population reacts positively to the histoplasmin skin test, the disease undoubtedly is endemic. Many instances of infection were missed until careful search was made. Fifty-four patients with mild attacks were discovered, and one died of systemic dissemination after therapy with cortisone.[257]

Among 1033 patients sent to the tuberculosis service of a Naval Hospital in New York State, 26 (2.5%) were found to have histoplasmosis. Two patients also had tuberculosis. Skin tests with tuberculin gave positive results in 95% of all patients, with histoplasmin in 20%, and with coccidioidin in 6%.[258]

Despite the danger of using cortisone in mycoses, the drug appeared to terminate histoplasmosis in two patients. Perhaps if its use is reserved for the treatment only of severe disease or administered late in the course after a degree of presumed immunity is established it may have a beneficial effect.[259] Therapeutic trials of ethyl vanillate, nystatin, and cycloheximide (Actidione) in 13 patients with chronic pulmonary histoplasmosis gave disappointing results, and the drugs often were toxic.[260]

Severe myocarditis with coccidioidal spherules in the muscle was observed in six patients. Three had pericarditis also, but the endocardium was not involved.[261] Evidently, Coccidioides immitis is one of the

many microbes able to cause myocardial lesions.

According to postmortem study of 15,845 patients between 1919 and 1955, there has been a striking increase in the number of secondary fungal infections, especially histoplasmosis, cryptococcosis, mucormycosis, moniliasis, and aspergillosis. In recent years, 30 of 40 of these patients had been treated with antimicrobics and 21 had lymphomas or leukemia.[262] Mucormycosis, caused by Rhizopus oryzae, probably is not a new disease but a newly recognized one. Since 1943, fourteen fatal cases have occurred in the United States. It usually attacks patients with diabetes, neoplasm, or other debilitating conditions. The onset may be incited by therapy with chemical agents, antimicrobics, or steroid hormones that depress resistance.[263] Vaccination with an autogenous vaccine and administration of iodine were suggested for therapy, although neither has any logical support.

Ten patients with blastomycosis were encountered in a six-week period in a community in North Carolina. The source and mode of spread were unknown. Skin tests with a specific antigen of 1600 other persons gave positive results in only 2.9%. Histoplasmin caused reactions in 6.4%, and tuberculin, in 25.6%.[264]

The subject of "athlete's foot" or pedal dermatophytosis was reopened by English investigators. They failed to find funguses in shower stalls or bath houses but feel that transmission of infection occurs by way of fragments of fungus-bearing skin.[265] Previously, American observers discounted contagion as a factor and indicated that funguses are habitually carried around and between the toes. They are saprophytes but become invasive in skin macerated by perspiration.

A case of endocarditis caused by Cryptococcus neoformans was described. The patient had rheumatic fever, and the fungus invaded the endocardium, meninges, and other organs. The symptoms resembled those of subacute bacterial endocarditis. Therapy with cycloheximide failed.[266]

Spirochetal Diseases

Leptospirosis.—Reports on leptospirosis in 159 papers were reviewed. Attention was drawn to the frequency of erroneous diagnosis because of the diverse clinical varieties of the disease and the high proportion of mild and anicteric attacks.[267] A review of the importance of leptospirosis in military forces appeared. There are about 70 types of leptospires.[268]

A laboratory aide accidentally inoculated himself with leptospires. Within one hour, 1,000,000 units (600 mg.) of penicillin was given orally, and 500,000 units (300 mg.) was given every six hours, for a total of 6,000,000 units (3600 mg.). On the eighth day, the original puncture wound became inflamed, and two days later fever and headache appeared, lasting three days. Leptospiremia was demonstrated. Evidently penicillin failed to prevent infection.[269] Pigs were an important source of infection with Leptospira canicola in five persons. On one farm 61% of samples of porcine blood contained specific antibody.[270]

Syphilis.—The original technique of the Treponema pallidum immobilization (TPI) test has been simplified for routine purposes in hospital laboratories. In a survey of 2500 serums tested with other methods in a year, 1772 gave falsely positive reactions. Of the latter, 40% gave reaction or weak reaction to the TPI test. These may have been the result of latent syphilis or may also have been falsely positive. Serums from patients diagnosed as having syphilis gave positive results in 72% of cases. The over-all agreement of clinical opinion with the TPI test was 61%.[271]

The present indications for applying the TPI test are (1) to distinguish between other false-positive and positive tests for syphilis, (2) to aid in diagnosis in the presence of clinical evidence of syphilis when the standard tests give negative results, and (3) to aid in diagnosis when epidemiologic evidence alone is present. A case in point was a congenitally syphilitic child whose blood failed to react with standard

tests but did with the TPI test.[272] With decrease in the incidence of syphilis, one may expect a relative increase in the number of false-positive reactions with standard tests. At present, the blood of 40% persons in the upper socioeconomic group gave falsely positive reactions in the absence of evidence of syphilis.[273] A general review of recent progress in the knowledge of syphilis appeared in the May and June, 1957, issues of the A. M. A. ARCHIVES OF INTERNAL MEDICINE.

The incidence in the United States of chancroid and lymphogranuloma venereum and inguinale declined by 70% of 80% in the last 10 years. The reported decline of syphilis was even greater, 94%. The downward trend may be partly ascribed to the eradication of the infections incidental to the widespread use of antimicrobic drugs for other diseases and to improved personal hygiene brought about by education and better socioeconomic conditions.[274]

Multiple Sclerosis.—Suggestion was made that multiple sclerosis is caused by a disturbance of normal immunologic processes. Arsenic was said to prevent progression of the disease, but controlled studies were not made.[275] Treponemes have been proposed as a cause since 1911 because of the remote resemblance of multiple sclerosis to syphilis. Spiral-shaped microorganisms, it was said, subsequently were demonstrated in the brain and spinal cord of victims. One investigator reported the cultivation of similar spiral forms from the spinal fluid of 78% of 76 patients by using a new medium for growth. None was obtained from 28 control patients.[276] The observations await confirmation.

Adrenal Steroids and Infections

Steroids should not be used in the treatment of mild or moderately severe infections. They have been used with apparent success for tuberculous meningitis, severe or overwhelming meningococcosis, typhoid, brucellosis, tetanus, viral hepatitis, herpes zoster, and mumps orchitis. In my experience, cortisone with chloramphenicol caused rapid clinical improvement in some patients with severe paratyphoid A but not in others.[194] Hormone therapy must always be accompanied by appropriate dosage of antimicrobics. The greatest value of steroids in infectious disease is for the relief of severe hypersensitive reactions to antimicrobic agents.[277]

Although cortisone has been used in severe tetanus, experimental studies gave evidence that it interfered with the therapeutic action of antitoxin and that it enhanced the effect of toxin in unprotected animals.[278] Cortisone injected two days before the inoculation of mice with Salmonella typhimurium greatly increased their susceptibility to infection. A single injection of 5 mg. reduced the survival rate from 100% to zero but was harmless in immunized mice.[279]

Steroid hormones were factors in causing the death of 19 patients among 400 who had received them. Four died of pneumonia; one, of peritonitis, and one, of septicemia.[280] Septic arthritis occurred in two patients in whom diagnosis was delayed because of suppressed signs or symptoms.[281] Three patients given cortisone therapy for other conditions had severe pneumonic varicella.[282] A curious event occurred in a patient treated with cortisone and oxytetracycline. He raised "bloody" sputum, but the color was caused by a heavy overgrowth of Serratia marcesens, a bacillus that has a brilliant red pigment.[283]

Adrenal steroids tend to suppress the dermal reaction of tuberculin. The opposite may occur. Twenty-four patients with various diseases did not react to the test. During treatment with cortisone or prednisolone, the reaction to tuberculin became positive. Perhaps the drugs in low dosage restored the ability to react which had been suppressed by age, infection, or adrenal insufficiency.[284]

Cortisone therapy in patients with trichinosis at times gave symptomatic relief. A

fatal case of eosinophilic myocarditis associated with trichinosis was described. Diagnosis was made post mortem.[285] Had clinical diagnosis been possible, perhaps cortisone therapy would have been beneficial, especially if myocarditis were allergic in origin. Rats infected with trichinellas and treated with cortisone had more larvas in their muscles than untreated ones. According to flocculation tests, untreated rats developed antibody, but those treated for 60 days did not.[286]

Urethral Catheters

Except under special circumstances, catheterization to obtain "clean" specimens of urine for culture should be abandoned. After careful cleaning of external parts, especially in female patients, urination usually provides suitable samples. No matter how carefully catheterization is done, there is danger of causing cystitis.[287,288] In 13 tests, tips of catheters were inserted into the urethra. When withdrawn, six of them bore Escherichia coli, staphylococci, or Aerobacter aerogenes. Urine should be examined microscopically and cultured on solid media, not in broth, to estimate the number of bacteria in urine. Bacteria demonstrated by catheterization do not always come from the bladder.[287] When samples of urine repeatedly yield Aerobacter, Proteus, Pseudomonas, or enterococci, it is likely that the patient has undergone instrumentation with or without prophylactic antimicrobics.[289]

A study of 651 major gynecologic operations revealed postoperative infections in 48%. Routine catheterization accounted for 25%, despite antimicrobic therapy.[290] About 20% of patients returned to their homes after surgical operation had pyuria or dysuria as a result of catheterization.[291]

Serratia marcesens applied deliberately to the urethral epithelium along indwelling catheters appeared in large numbers in the urine in one to three days. They probably entered the bladder by way of an exudate around the instrument.

Bacteria implanted in the bladder by catheterization may enter the blood. Infection is more apt to occur when catheters are left in place for days. Antimicrobic therapy often fails after sensitive bacteria are replaced by resistant ones.[289]

The demonstration of bacteria in specimens of urine does not always indicate their pathogenic activity. By means of a small catheter held in the sleeve of a larger one, fewer bacterial growths (32%) were obtained than with a large catheter alone (52%).[292] The insertion of small catheters may reduce the incidence of iatrogenic cystitis.

Miscellaneous Subjects

Psittacosis.—Seven members of a physician's family in Norway had psittacosis in varying degrees of severity. The source of infection was not discovered, but person-to-person transmission was suspected.[293] Pigeons were the source of ornithosis in German victims.[294]

Rocky Mountain Spotted Fever.—Rocky Mountain spotted fever was reported in 2239 patients in the southeastern United States. This number was slightly less than that recorded in the rest of the country. The name obviously is a misnomer. Seventy-four cases were studied in a Virginian hospital in a 10-year period. Patients were of all ages and usually came from rural areas. Most of them had removed ticks from dogs. There were seven deaths, chiefly in victims older than 55.[295]

Listeriosis.—Ten cases of meningitis caused by Listeria monocytogenes were described.[296,297] Four recovered after therapy. The germ varies greatly in sensitivity to different antimicrobics and is easily confused with diphtheroids and streptococci. One patient's blood caused cold agglutination of erythrocytes. The reaction may be confused with the heterophil antibody response and account for difficulty in differentiating listeriosis from infectious mononucleosis.[298]

Pleuropneumonia-like microbes may be causally related to acute abacterial pyuria and hemorrhagic cystitis. A patient had involvement of the urethra, eyes, joints, and skin. A relationship to Reiter's disease was proposed.[299]

Amebiasis.—According to Kean, there is no acceptable evidence to show the existence of acute hepatitis of amebic origin comparable with the diffuse focal lesions found in typhoid or brucellosis. The only proved amebic hepatic involvement is single or multiple abscess. Hepatitis, if present, may be due to other cause.[300] Manson-Bahr rejects intradermal or serologic tests as unreliable for the diagnosis of colonic amebiasis. Rectal biopsy specimens or scrapings of the mucosa are preferable and are as dependable for diagnosis as similar specimens are in the case of schistosomiasis. Diagnosis was made from scrapings in seven patients whose stools contained no cysts.[301]

Study of 400 cases of acute and chronic schistosomiasis (mansoni) was made in Puerto Rico. The acute phase usually was mild or inapparent and dominated by a reaction of hypersensitivity. Fulminating attacks occurred only in heavily infected or poorly nourished victims. The severity of the later lesions of chronic infection depended largely on the defensive mechanism of the host, and death with, not due to, schistosomiasis was the general rule. There are no specific therapeutic agents.[302]

Other Protozoal Infections.—Antimicrobics failed to influence fever and an increased amount of protein in the spinal fluid of a newborn infant. A dye test and the complement-fixation test indicated toxoplasmosis. Both tests gave negative results three years later. Apparently the patient had recovered.[303] Because of its greater simplicity, the hemagglutination test may replace the dye test for diagnosis.[304]

What was said to be the first human case of sarcosporidiosis in which diagnosis was confirmed by the complement-fixation test was described.[305] In this instance, periarteritis seemed to be related to the infection, as it was in cases of trichinosis described in 1943. About 300 cases of isosporosis are on record, 27 in the United States. The infection is endemic in the Mediterranean regions. Three more cases were reported on from Tennessee, but diagnosis apparently was made only on the basis of oocysts in the stool. At necropsy in one patient, nothing was reported to substantiate pathogenicity of the protozoan.[306] Pneumocystis carinii causes a form of interstitial plasma-cell pneumonia in premature or debilitated European children. Only one authenticated case was said to have been detected in the United States. It is uncertain whether the micro-organism described by Chagas in 1909 is a protozoan or a fungus. Knowledge of the subject was reviewed by Gajdusek.[307]

Helminthiasis.—Political unrest and migration of persons from exotic regions to this country and the large number of Americans who have been abroad have increased the incidence of helminthic diseases in the United States. Negroes moving northward carry with them hookworms, whipworms, and ascariasis. Puerto Ricans bring schistosomiasis and filariasis. Strongyloides appeared in Chicago. The application of sanitary and hygienic measures limits the spread of these parasites. They are not apt to become endemic. The diseases they cause, if unsuspected, may not be correctly diagnosed.[308]

Cysticercosis is encountered rarely, but three cases were seen in Boston.[309] Cerebral localization occurs many years after the primary entrance of the worm and seldom is diagnosed clinically unless the possibility is kept in mind. The disease is endemic in India, South America, and elsewhere. Sixty-five cases of cerebral cysticercosis, with a discussion of its clinical behavior, diagnosis, and treatment, were reported on from Rumania.[310] A new broad-spectrum anthelmintic, dithiazanine, was introduced.[311]

Resistance to Infection.—Chandler reviewed the complex relationship between nutrition and infection. Malnutrition interferes with the host's response to infection, and, conversely, infections and their treatment have adverse effects on nutrition. Adequate intake of food is basic to natural and acquired resistance. Education and improvement of the environment and economic conditions are of primary importance. Residual sprays, drug therapy, and vaccination to control infectious diseases are of value, but "they are like putting pans under leaking pipes instead of mending the pipes." They impress "political administrators because of their short-term spectacular effects." [312]

Knowledge of the effects of total acute body irradiation on infection was reviewed. Antimicrobics should not be used prophylactically but only when need arises. As yet, no prophylactic or therapeutic agents other than antimicrobics should be kept in stock for the management of hematologic depression from possible atomic warfare.[313] Review was made of the danger of infection in children whose spleens have been excised. Fulminating and fatal infections have occurred 1 to 12 years after splenectomy.[314]

Lymph nodes from a normal person were implanted into a person with hypoglobulinemia and no demonstrable humoral antibodies. Antityphoid vaccine injected at three intervals of seven days then evoked specific antibody. The transplanted lymph nodes apparently atrophied in about five months, but sensitivity to tuberculin acquired from the donor persisted for several more months.[315]

Mesenteric Adenitis.—Acute appendicitis and mesenteric adenitis may be difficult to differentiate. Until methods for specific diagnosis are devised, the history of an attack, physical findings, and clinical judgment must be depended upon. In a survey of about 200 cases of mesenteric adenitis, abdominal rigidity was present in 18 and the leukocytes numbered less than 10,000 per cubic millimeter in 52% and more than 16,000 in 19%. The onset was preceded by or accompanied with symptoms of a cold in 67%. Acute appendicitis also may occur during a cold. Generalized or regional lymph node swelling occurred in 55%. More than half of the patients had had similar previous attacks.[316]

As a sequel to Coldrey's report on the conservative nonsurgical treatment of acute appendicitis, Louttit described two patients successfully treated with penicillin and streptomycin. The method may be applicable in circumstances where prompt surgical excision is not possible or is resisted.[317]

Bronchiectasis.—A committee arranged for the division of 122 bronchiectatic patients into three groups. One group was treated with penicillin; another, with oxytetracycline, and the third, with lactose. In each group the volume of sputum was reduced. Penicillin was helpful in a few, and oxytetracycline gave the best results, even though its effect was less striking. Relapse occurred after treatment was stopped. Therapy for a year with oxytetracycline cost £60 per patient and was recommended only for far-advanced disease.[318]

Snuff containing Proteus vulgaris and Pseudomonas aeruginosa appeared to be the source of infection in a patient with chronic bronchitis.[319]

Other Subjects.—Pseudomonas, Flavobacterium, Achromobacter, Corynebacterium, Staphylococci, and Sarcina were cultivated from samples of air collected 9000 ft. over the ocean. Similar bacteria were present over areas of land.[320] The subject of contact and airborne infections was reviewed. Of 108 infections listed, 22 are chiefly airborne.[321] Animals used for laboratory studies should not be regarded as uncontaminated test tubes. They may harbor a variety of infectious agents as listed by Innes, which confuse experimental studies.[322] Roentgen therapy never had much value in the treatment of infections. With the advent of modern drugs, its use should be abandoned for pyogenic infections, moniliasis, and granulomas.[323]

Great progress made in the field of infectious diseases by Russians was summarized by Meyer after a visit to the U. S. S. R.[324] This report and the quality and quantity of investigative work published in abstract form in English attest to the high standard of medical research there today. One has only to peruse issues of the *Journal of Microbiology, Epidemiology and Immunobiology; Problems of Virology,* and *Abstracts of Soviet Medicine* to gain an idea of the work in progress. Yet sparse reference is made and little credit is given in these publications to non-Russian scientific contributions.

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REFERENCES

1. F. T. C. Digs Deeper into Drug Prices, The New York Times, May 26, 1957.

2. Welch, H.: Problems of Antibiotics in Food as the Food and Drug Administration Sees Them, Am. J. Pub. Health 47:701-705 (June) 1957.

3. Nolen, W. A., and Dille, D. E.: Use and Abuse of Antibiotics in a Small Community, New England J. Med. 257:33-34 (July 4) 1957.

4. Kinney, J. R.: The Prevalence of Antibiotically Treated People, Ann. Int. Med. 47:71-77 (July) 1957.

5. Antibiotics in Virus Diseases, Editorials, J. A. M. A. 165:53-54 (Sept. 7) 1957.

6. Dowling, H. F., et al.: The Clinical Use of Antibiotics in Combination, Editorials, A. M. A. Arch. Int. Med. 99:536-538 (April) 1957.

7. Dowling, H. F.: Mixtures of Antibiotics, J. A. M. A. 164:44-48 (May 4) 1957.

8. Oleandomycin-Tetracycline Mixture, Editorials, New England J. Med. 257:289-290 (Aug. 8) 1957.

9. Erythromycin, Oleandomycin and Spiramycin —and Their Combinations with Tetracycline, Editorials, New England J. Med. 257:525-526 (Sept. 12) 1957.

10. The Staphylococcus Plague, Leading Articles, Lancet 1:723 (April 6) 1957.

11. Jones, W. F., Jr., and Finland, M.: Antibiotic Combinations: Antibacterial Action of Plasma of Normal Subjects After Oral Doses of Penicillin V, Tetracycline Hydrochloride and a Combination of Both, New England J. Med. 256: 869-875 (May 9) 1957.

12. Levitt, R. O., and Hubble, R. H.: Antibiotic Mixtures: In Vitro Effect of a Tetracycline-Oleandomycin Mixture (PA 775) on Staphylococci, New England J. Med. 257:180-181 (July 25) 1957.

13. Jones, W. F., Jr., and Finland, M.: Antibiotic Combinations: Antistreptococcal and Antistaphylococcal Activity of Normal Subjects After Ingestion of Erythromycin or Chloramphenicol or Both, New England J. Med. 257:744-748 (Oct. 17) 1957.

14. Jones, W. F., Jr., and Finland, M.: Antibiotic Combinations: Tetracycline, Erythromycin, Oleandomycin and Spiramycin and Combinations of Tetracycline with Each of the Other Three Agents—Comparisons of Activity in Vitro and Antibacterial Action of Blood After Oral Administration, New England J. Med. 257:481-491 (Sept. 12); 536-547 (Sept. 19) 1957.

15. Garrod, L. P.: Terramycin and Aureomycin, Reviews, Brit. M. J. 1:1404-1405 (June 15) 1957.

16. Koch, R., and Hanson, H.: Treatment of Acute Purulent Meningitis with Tetracycline, J. Pediat. 51:65-73 (July) 1957.

17. Breese, B. B.; Disney, F. A., and Talpey, W. B.: Novobiocin in the Treatment of Beta-Hemolytic Streptococcal Infections in Children, Antibiotic Med. & Clin. Ther. 4:347-351 (June) 1957.

18. Romansky, M. J.; Nasow, J. P.; Davis, D. S., and Ritts, R. E., Jr.: Clinical Spectrums of Erythromycin as Evaluated in 260 Patients, J. A. M. A. 164:1197-1204 (July 13) 1957.

19. Siminoff, P.; Smith, R. M.; Sokolski, W. T., and Savage, G. M.: Streptovaricin: I. Discovery and Biologic Activity, Am. Rev. Tuberc. 75:576-583 (April) 1957.

20. Nichols, R. L.; Richards, W. A., and Finland, M.: Penicillin and Probenecid: A Controlled Study of Penicillin Levels in Plasma of Patients with Bacterial Endocarditis, Am. J. M. Sc. 233: 245-255 (March) 1957.

21. Reynolds, E. S.: Schlant, R. C.; Gonick, H. C., and Dammin, G. J.: Fatal Massive Necrosis of the Liver as a Manifestation of Hypersensitivity to Probenecid, New England J. Med. 256:592-596 (March 28) 1957.

22. Waisbren, B. A.: The Treatment of Bacterial Infections with the Combination of Antibiotics and Gamma Globulin, Antibiotics & Chemother. 7:323-327 (June) 1957.

23. Burdick, K. H.: Reactions to Prophylactically Administered Penicillin: A Study of 68 Hospitalized Patients, U. S. Armed Forces M. J. 8:528-533 (April) 1957.

24. Antibiotics, Symposia, Lancet 2:888-889 (Nov. 2) 1957.

25. Minno, A. M., and Davis, G. M.: Penicillinase in the Treatment of Penicillin Reactions, J. A. M. A. 165:222-224 (Sept. 21) 1957.

26. Smith, V.: Fatal Reactions to Penicillin: Evaluation of a Test for Sensitivity, New England J. Med. 257:447-451 (Sept. 5) 1957.

27. Hahn, F. E., and Ciak, J.: Penicillin-Induced Lysis of Escherichia Coli, Science 125:119-120 (Jan. 18) 1957.

28. Mudd, S.: Clues to the Rational Preparation of Antibacterial and Antiviral Agents, Editorials, J. A. M. A. 163:1142 (March 30) 1957.

29. Total Synthesis of a Penicillin, Annotations, Lancet 1:815 (April 6) 1957.

30. Poth, E. J.: Critical Analysis of Intestinal Antisepsis, J. A. M. A. 163:1317-1322 (April 13) 1957.

31. Griffiths, E.: Failure of Penicillin to Prevent Post-Operative Chest Infection, Brit. M. J. 1:803-804 (April 6) 1957.

32. Kapp, D. F.: Antibiotic Prophylaxis in Unpredictable Infections: A Medical and Surgical Fallacy, Guthrie Clin. Bull. 26:165-168 (April) 1957.

33. Drake, M. E.: Antibiotics and Chemotherapy in Treatment of Respiratory Infections, J. M. Soc. New Jersey 54:63-65 (Feb.) 1957.

34. Petersdorf, R. G., et al.: A Study of Antibiotic Prophylaxis in Unconscious Patients, New England J. Med. 257:1001-1009 (Nov. 21) 1957.

35. Torak, R. M.: Fungus Infections Associated with Antibiotic and Steroid Therapy, Am. J. Med. 22:872-882 (June) 1957.

36. Wickerham, L. J.: Apparent Increase in Frequency of Infections Involving Torulopsis Glabrata: Procedure for Its Identification, J. A. M. A. 165:47-48 (Sept. 7) 1957.

37. Roth, F. J., and Murphy, W. H.: Lethality of Cell-Free Extract of Candida Albicans for Chlortetracycline Treated Mice, Proc. Soc. Exper. Biol. & Med. 94:530-532 (March) 1957.

38. Catterall, R. D., and Nicol, C. S.: Systemic Treatment of Trichomonal Infections, Brit. M. J. 2:29-31 (July 6) 1957.

39. Evans, A. S.: Acute Respiratory Disease in University of Wisconsin Students, New England J. Med. 256:377-384 (Feb. 28) 1957.

40. Breese, B. B., and Morgan, H. R.: A Study of an Epidemic of Respiratory Infections of Multiple Etiology, New York J. Med. 57:1918-1920 (June 1) 1957.

41. Pelon, W.; Mogabgab, W. J.; Phillips, I. A., and Pierce, W. E.: A Cytopathogenic Agent Isolated from Naval Recruits with Mild Respiratory Illnesses, Proc. Soc. Exper. Biol. & Med. 94:262-267 (Feb.) 1957.

42. Price, W. H.: Proc. Nat. Acad. Sc. (Sept.) 1957.

43. A Common-Cold Vaccine? Annotations, Lancet 2:682 (Oct. 5) 1957.

43a. Ritchie, J. M.: Autogenous Vaccine in Prophylaxis of the Common Cold, Lancet 1:615-618 (March 22) 1958.

43b. Ritchie, J. M.: Antibiotics in Small Doses for the Common Cold, Lancet 1:618-621 (March 22) 1958.

43c. Common Cold: New Attack, Time Magazine (Atlantic Ed.) April 14, 1958, p. 39.

44. Kendal, E. J., et al.: Pharnygo-Conjunctival Fever: School Outbreaks in England During the Summer of 1955 Associated with Adenovirus Types 3, 7, and 14, Brit. M. J. 2:131-136 (July 20) 1957.

45. McFarlane, P. S., and Sommerville, R. G.: Nontuberculous Juvenile Bronchiectasis: A Virus Disease? Lancet 1:770-771 (April 13) 1957.

46. Hilleman, M. R.; Hodges, R. E.; Warfield, M. S., and Anderson, S. A.: Acute Respiratory Illness in Volunteers Following Intramuscular Administration of Live Adenovirus, J. Clin. Invest. 36:1072-1080 (July) 1957.

47. Hilleman, M. R., et al.: Vaccination Against Acute Respiratory Illness of Adenovirus (RI-APC-ARD) Etiology, Am. J. Pub. Health 47: 841-847 (July) 1957.

48. Johnston, P. B.; Grayston, J. T., and Loosli, C. G.: Adenovirus Neutralizing Antibody Determination by Colorimetric Assay, Proc. Soc. Exper. Biol. & Med. 94:338-343 (Feb.) 1957.

49. Friedman, M., and Bennett, C. R.: A Hemagglutination Test for Detection of Adenovirus Antibodies, Proc. Soc. Exper. Biol. & Med. 94:712-717 (April) 1957.

50. Fisher, T. N., and Ginsberg, H. S.: Accumulation of Organic Acids by HeLa Cells Infected with Type 4 Adenovirus, Proc. Soc. Exper. Biol. & Med. 95:47-51 (May) 1957.

51. Collins, S. D., and Lehmann, J. L.: Influenza Epidemics During 1951-56, with a Review of Trends, Pub. Health Rep. 72:771-780 (Sept.) 1957.

52. Meenan, P. N.; Clarke, M., and Byrne, F. E.: Influenza Between Epidemics, Lancet 1:923-925 (May 4) 1957.

53. Zakstel'skaia, L. I.: Asymptomatic Carriage of Influenza Virus, Problems Virol. 2:31-36, 1957.

54. Jensen, K. E.: New Set of Type A Influenza Viruses, J. A. M. A. 164:2025-2029 (Aug. 31) 1957.

55. Influenza Virus Variants, Leading Articles, Lancet 1:1517-1518 (June 29) 1957.

56: Sommerville, R. G.: Newborn Pneumonitis Virus (Type Sendai): Evidence of Infection in South West Scotland, Brit. M. J. 1:1145-1148 (May 18) 1957.

57. Gardner, P. S.: Serological Evidence of Infection with Sendai Virus in England, Brit. M. J. 1:1143-1145 (May 18) 1957.

58. Grist, N. R.; Sommerville, R. G., and Carson, H. G.: Respiratory Virus Infection in Hospital and in General Practice, 1954-6, Brit. M. J. 1:378-380 (Feb. 16) 1957.

59. White, G. B.; Gardner, P. S., and Simpson, R. E. H.: Infection with Sendai Virus in an Outbreak of Respiratory Illness, Brit. M. J. 1:381-383 (Feb. 16) 1957.

60. The New York Times, Sept. 11 and 14, 1957.

61. Giles, C., and Shuttleworth, E. M.: Post-Mortem Findings in 46 Influenza Deaths, Lancet 2:1224-1225 (Dec. 14) 1957.

62. Goslings, W. R. O.; Masurel, N., and Mulder, J.: Death from Asiatic Influenza in the Netherlands, Lancet 2:1164-1165 (Dec. 7) 1957.

63. Culver, J. O.; Nitz, R. E., and Lennette, E. H.: The Protective Effect of Monovalent Asian-Strain Vaccine Against Asian Influenza, J.A.M.A. 165:2174-2177 (Dec. 28) 1957.

64. Vaccination Against Asian Influenza: Basis for Recommendation and a Preliminary Report on Efficacy, J. A. M. A. 165:2055-2058 (Dec. 21) 1957.

65. Current Status of Asian Influenza, J.A.M.A. 165:59 (Sept. 7) 1957.

66. Clinical Trials of Influenza Vaccine: Third Progress Report to the Medical Research Council by Its Committee on Clinical Trials of Influenza Vaccine, Brit. M. J. 2:1-7 (July 6) 1957.

67. Fotin, A. V.: The Condition of the Nasal Mucosa in Virus Influenza, Abstr. Soviet Med. 1:115, 1957.

68. Holtz, G., and Bang, F. B.: Electron Microscope Studies of Ferret Respiratory Cells Infected with Influenza, Bull. Johns Hopkins Hosp. 101:175-208 (Oct.) 1957.

69. Channock, R. M.: Association of a New Type of Cytopathogenic Myxovirus with Infantile Croup, J. Exper. Med. 104:555-575 (Oct.) 1956.

70. Liu, C., and Heyl, J. T.: Serological Study of Primary Atypical Pneumonia, Fed. Proc. 16: 423 (March) 1957.

71. Andrews, R. H.: Pneumonia and Bronchial Vesiculation Associated with Herpes Zoster, with Reference to Other Visceral Associations of Zoster, Brit. M. J. 2:384-386 (Aug. 17) 1957.

72. Sheldon, G. C., and Smellie, H.: Cat-Scratch Disease with Pneumonia, Brit. M. J. 2:446-447 (Aug. 24) 1957.

73. Marinesco, G.: Interstitial Pneumonia in Poliomyelitis, Press méd. 64:2207-2210 (Dec. 25) 1956.

74. Bates, R. C.; Jennings, R. B., and Earle, D. P.: Acute Nephritis Unrelated to Group A Hemolytic Streptococcus Infection, Report of 10 Cases, Am. J. Med. 23:510-528 (Oct.) 1957.

75. Vought, R. L., and Greenberg, M.: Natural Immunization Against Poliomyelitis: Effectiveness as Measured by Mortality from the Disease in Successive Generations of Children, 1915-1934, J. A. M. A. 164:1050-1053 (July 6) 1957.

76. Payzin, S., and Murray, E. S.: Note on Antibodies to Poliomyelitis Viruses in the Sera of Residents of Eastern Saudi Arabia, Am. J. Trop. Med. 6:704-706 (July) 1957.

77. Bernkopf, H.; Medalie, J., and Yekutiel, M.: Antibodies to Poliomyelitis Virus and Socio-economic Factors Influencing Their Frequency in Children in Israel, Am. J. Trop. Med. 6:697-703 (July) 1957.

78. Snell, B.; Balducci, D., and Tyrrell, D. A. J.: "Polioencephalitis": A Clinical and Laboratory Study, Brit. M. J. 2:126-128 (July 20) 1957.

79. Doll, R., and Hill, A. B.: Deaths from Poliomyelitis Among British Doctors, Brit. M. J. 1:372 (Feb.) 1957.

80. Thorner, R. M., and Bond, J. O.: Pertussis in Florida, J. Pediat. 72:795-800 (Sept.) 1957.

81. The Outlook in Poliomyelitis, Statist. Bull. Metrop. Life Insur. Co. 38:1-4 (Aug.) 1957.

82. Bundesen, H. N.; Graning, H. M.; Goldberg, E. L., and Bauer, F. C.: Preliminary Report and Observations On the 1956 Poliomyelitis Outbreak in Chicago, with an Evaluation of the Large-Scale Use of Salk Vaccine, Particularly in the Face of a Sharply Rising Incidence, J. A. M. A. 163:1604-1619 (April 27) 1957.

83. Ratner, H.: Stalking the Salk, Letters from Our Readers, GP 15:21-25 (May) 1957.

84. The Assessment of the British Vaccine Against Poliomyelitis: A Report to the Medical Research Council by Its Poliomyelitis Vaccine Committee, Brit. M. J. 1:1271-1277 (June 1) 1957.

85. The New York Times, Oct. 11, 1957, p. 29.

86. Nathanson, N.; Hall, W. J.; Thrupp, L. D., and Forester, H.: Surveillance of Poliomyelitis in the United States in 1956, Pub. Health Rep. 72: 381-392 (May) 1957.

87. Gelfand, H. M.; Fox, J. P., and LeBlanc, D. R.: Observations on Natural Poliovirus Infections in Immunized Children, Am. J. Pub. Health 47:421-431 (April) 1957.

88. Howe, H. A.: Day-by-Day Response of Vaccinated Chimpanzees to Poliomyelitic Infection, Am. J. Pub. Health 47:871-875 (July) 1957.

89. Horstmann, D. M.; Niederman, J. C.; Melnick, J. L., and Paul, J. R.: Poliomyelitis: Comparison of Responses of Vaccinated and Naturally Immune Humans to Ingestion of Attenuated Poliovirus, Tr. A. Am. Physicians 70:91-101, 1957.

90. Lipman, W. H.: Allergic Reactions to the Salk Poliomyelitis Vaccine, GP 15:95-98 (Feb.) 1957.

91. Habel, K., and Loomis, L. N.: Coxsackie A7 Virus and the Russian "Poliovirus Type 4," Proc. Soc. Exper. Biol. & Med. 95:597-605 (July) 1957.

92. Macrae, A. D.: Poliomyelitis Studies in an Isolated Scottish Community, Brit. M. J. 1:368-372 (Feb. 16) 1957.

93. Rivadeneira, J. C.; Robbins, F. C.; Crea, M., and Eiben, R. M.: The Distribution of Group

B Coxsackie Viruses in a Children's Institution, Pediatrics 20:468-476 (Sept.) 1957.

94. Gelfand, H. M.; Fox, J. P., and LeBlanc, D. R.: The Enteric Viral Flora of a Population of Normal Children in Southern Louisiana, Am. J. Trop. Med. 6:521-531 (May) 1957.

95. Syverton, J. T., et al.: Outbreak of Aseptic Meningitis Caused by Coxsackie B5 Virus: Laboratory, Clinical, and Epidemiologic Study, J. A. M. A. 164:2015-2019 (Aug. 31) 1957.

96. Weinstein, S. B.: Acute Benign Pericarditis Associated with Coxsackie Virus Group B, Type 5, New England J. Med. 257:265-267 (Aug. 8) 1957.

97. Shelokov, A., and Habel, K.: Viremia in Coxsackie B Meningitis, Proc. Soc. Exper. Biol. & Med. 94:782-784 (April) 1957.

98. Howlett, J. G., and Somlo, F.: A New Syndrome of Parotitis with Herpangina Caused by the Coxsackie Virus, Canad. M. A. J. 77:5-7 (July 1) 1957.

99. Langsdale-Smith, H. G.; Langsdale-Smith, D. M., and Wilkinson, B. R.: Epidemic of Meningoencephalitis and Bornholm Disease, Brit. M. J. 1:805-806 (April 6) 1957.

100. Laforest, R. A., et al.: Outbreak of Aseptic Meningitis (Meningoencephalitis) with Rubelliform Rash: Toronto, 1956, Canad. M. A. J. 77:1-4 (July 1) 1957.

101. von Oldershausen, H. F.: Clinical Observations on a New Type of Primary Aseptic Meningoencephalitis (Epidemic Viral Meningoencephalitis), Deutsche. med. Wchnschr. 82:442-447 (March 29) 1957.

102. Baumann, T., et al.: Diseases Caused by ECHO-Virus Type 9: Epidemiological Clinical and Virological-Serological Study, Schweiz. med. Wchnschr. 87:307-315 (March 30) 1957.

103. Quersin-Thiry, L.; Nihoul, E., and Dekking, F.: ECHO Virus Type 9 (New Member of Coxsackie Group Type A?) as a Cause of Epidemic Meningitis, Science 125:744-745 (April 19) 1957.

104. McLean, D. M., and Melnick, J. L.: Association of Mouse Pathogenic Strain of Echo Virus Type 9 with Aseptic Meningitis, Proc. Soc. Exper. Biol. & Med. 94:656-660 (April) 1957.

105. Eichenwald, H. F.; Ababio, A.; Arky, A. M., and Hartman, A. P.: Epidemic Diarrhea in Premature Infants Caused by a Cytopathogenic Enteric Virus, Abstract, A. M. A. J. Dis. Child. 94:540-541 (Nov.) 1957.

106. Stulberg, C. S.; Zuelzer, W. W., and Page, R. H.: The Significance of Cytopathogenic Agents in Epidemic and Sporadic Diarrhea of Infancy, Abstract, A. M. A. J. Dis. Child. 94:568 (Nov.) 1957.

107. New Bovine Viral Agents Isolated in Michigan, Pub. Health Rep. 72:251-252 (March) 1957.

108. Galpine, J. T., and Brady, C.: Benign Myalgic Encephalomyelitis, Lancet 1:757-758 (April 13) 1957.

109. Shelokov, A.; Habel, K.; Verder, E., and Welsh, W.: Epidemic Neuromyasthenia: An Outbreak of Poliomyelitislike Illness in Student Nurses, New England J. Med. 257:345-355 (Aug. 22) 1957.

110. Poskanzer, D. C., et al.: Epidemic Neuromyasthenia: An Outbreak in Punta Gorda, Florida, New England J. Med. 257:356-364 (Aug. 22) 1957.

111. An Outbreak of Encephalomyelitis in the Royal Free Hospital Group, London, in 1955, Brit. M. J. 2:895-904 (Oct. 19) 1957.

112. Hanson, R. P.: An Epizootic of Equine Encephalomyelitis that Occurred in Massachusetts in 1831, Am. J. Trop. Med. 6:858-862 (Sept.) 1957.

113. Feemster, R.: Equine Encephalitis in Massachusetts, New England J. Med. 257:701-704 (Oct. 10) 1957.

114. Paxson, E. M., and McKay, R. J.: Neurologic Symptoms Associated with Cat Scratch Disease, Pediatrics 20:13-22 (July) 1957.

115. Habel, K.: Rabies Prophylaxis in Man, Pediatrics 19:923-936 (May) 1957.

116. Habel, K.: Rabies Prophylaxis in Man, Pub. Health Rep. 72:667-673 (Aug.) 1957.

117. McDaniel, G. E.: Experiences in the Treatment of Human Beings with Antirabic Vaccine in South Carolina, South. M. J. 50:1369-1371 (Nov.) 1957.

118. Meyer, K. F.: Man Contracting Rabies from Man, Editorials, J. A. M. A. 165:158-159 (Sept. 14) 1957.

119. Schneider, N. J., et al.: Rabies in Bats in Florida, Am. J. Pub. Health 47:983-989 (Aug.) 1957.

120. Tyler, H. R.: Neurological Complications of Rubeola (Measles), Medicine 36:147-167 (May) 1957.

121. Enders, J. F., et al.: Measles Virus: A Summary of Experiments Concerned with Isolation, Properties, and Behavior, Am. J. Pub. Health 47:275-282 (March) 1957.

122. Milovanovic, M. V.; Enders, J. F., and Mitus, A.: Cultivation of Measles Virus in Human Embryo Amnion Cells and in Developing Chick Embryo, Proc. Soc. Exper. Biol. & Med. 95:120-127 (May) 1957.

123. Greenberg, M.; Pellitteri, O., and Barton, J.: Frequency of Defects in Infants Whose Mothers Had Rubella During Pregnancy, J.A.M.A. 165:675-678 (Oct. 12) 1957.

124. Krugman, S.; Goodrich, C. N., and Ward, R.: Primary Varicella Pneumonia, New England J. Med. 257:843-848 (Oct. 31) 1957.

125. Utz, J. P., et al.: Clinical and Laboratory Studies of Mumps: I. Laboratory Diagnoses by Tissue-Culture Technics, New England J. Med. 257:497-502 (Sept. 12) 1957.

126. Eylan, E., and Zmucky, R.: Mumps Virus and Subacute Thyroiditis: Evidence of a Causal Association, Lancet 1:1062-1063 (May 25) 1957.

127. Katz, R.; Ducci, H.; Bennett, H., and Rodriguez, J.: Incidence of Hepatitis Following Transfusions of Whole Blood, Am. J. Clin. Path. 27:406-421 (April) 1957.

128. Shaldon, S., and Sherlock, S.: Virus Hepatitis with Features of Prolonged Bile Retention, Brit. M. J. 2:734-738 (Sept. 28) 1957.

129. Nelson, R. S.: Present Indications for Cortisone Therapy in Acute Viral Hepatitis, Ann. Int. Med. 46:685-695 (April) 1957.

130. Thaler, H.; Benda, L., and Rissel, E.: Histologic Changes in Viral Hepatitis Studied by Liver Biopsy, Gastroenterology 33:209-224 (Aug.) 1957.

131. Dische, F. E., and Golding, J. R.: Agranulocytosis Associated with Infectious Hepatitis, Brit. M. J. 2:738-740 (Sept. 28) 1957.

132. Poff, N. L., and Laurence, R., Jr.: Spontaneous Rupture of the Spleen in Infectious Mononucleosis, A. M. A. Arch. Int. Med. 100: 311-313 (Aug.) 1957.

133. McLaughlan, G. P.: Epidemic Vomiting: A Study of Several Outbreaks, M. Officer 97:47-53 (Jan. 25) 1957.

134. Tateno, I., et al.: On an ECHO-like Agent Constantly Recoverable from Volunteers Given Niigata Strain of Acute Epidemic Gastroenteritis, Jap. J. Exper. Med. 26:125-138 (Aug.) 1956.

135. Burgoon, C. F., Jr.; Burgoon, J. S., and Baldridge, G. D.: The Natural History of Herpes Zoster, J. A. M. A. 164:265-269 (May 18) 1957.

136. de Moragas, J. M., and Kierland, R. R.: The Outcome of Patients with Herpes Zoster, A. M. A. Arch. Dermat. 75:193-196 (Feb.) 1957.

137. Wyburn-Mason, R.: Visceral Lesions in Herpes Zoster, Brit. M. J. 1:678-681 (March 23) 1957.

138. Zeitlenok, N. A.; Vanag, K. A., and Pille, E. R.: Cases of Illness of the Crimean Haemorrhagic Fever Type Observed in the Astrakhan Oblast, Problems Virol. 2:90-96, 1957.

139. Evans, A. D.; Pallis, C. A., and Spillane, J. D.: Involvement of Nervous System in Behcet's Syndrome: Report of 3 Cases and Isolation of Virus, Lancet 2:349-353 (Aug. 24) 1957.

140. McMenemey, W. H., and Lawrence, B. J.: Encephalomyelopathy in Behcet's Disease: Report of Necropsy Findings in 2 Cases, Lancet 2:353-358 (Aug. 24) 1957.

141. Sprunt, K.: Newly Isolated Viruses as Causes of Disease, Am. J. M. Sc. 233:688-708 (June) 1957.

142. Virus Meningitis and Encephalomyelitis, Leading Articles, Brit. M. J. 1:811-813 (April 6) 1957.

143. Huebner, R. J.: Implications of Recent Viral Studies, Pub. Health Rep. 72:377-380 (May) 1957.

144. Burnet, M.: Cancer—a Biological Approach: III. Viruses Associated with Neoplastic Conditions, Brit. M. J. 1:841-847 (April 13) 1957.

145. Viruses Made to Order, Editorials, Brit. M. J. 1:390-391 (Feb. 16) 1957.

146. Kissling, R. E.: Growth of Several Arthropod-Borne Viruses in Tissue Culture, Proc. Soc. Exper. Biol. & Med. 96:290-294 (Nov.) 1957.

147. Barsky, J.; Kourilsky, R., and Cornefert, F.: Resistance of Respiratory Ciliated Epithelium to Action of Polio and Adeno Viruses in Vitro, Proc. Soc. Exper. Biol. & Med. 96:386-391 (Nov.) 1957.

148. Evans, A. S.: Establishment of Human Adult Tonsil Cells in Continuous Culture and Their Virus Susceptibilities, Proc. Soc. Exper. Biol. & Med. 96:752-757 (Dec.) 1957.

149. Dubos, R. J.: Medicine, The Rockefeller Institute Bulletin, Annual Report, 1955-1956, pp. 69-71.

150. Hsu, K. H.-K.: Diagnosis and Antimicrobial Therapy of Primary Tuberculosis in Children, J. A. M. A. 164:1204-1209 (July 13) 1957.

151. Myers, J. A.; Boynton, R. E., and Diehl, H. S.: Tuberculosis Among University Students: A 35-Year Experience, Ann. Int. Med. 46:201-217 (Feb.) 1957.

152. Marsh, K.: Tuberculosis Among the Residents of Hostels and Lodging Houses in London, Lancet 1:1136-1138 (June 1) 1957.

153. Tattersall, W. H.: Tuberculosis Case Finding in a Reception Center, Lancet 1:1138-1139 (June 1) 1957.

154. Reid, D. D.: Incidence of Tuberculosis Among Workers in Medical Laboratories, Brit. M. J. 2:10-14 (July 6) 1957.

155. Gale, G.: Accidental Infection with Tubercle Bacilli in Laboratory Technicians, Canad. M. A. J. 76:646-648 (April 15) 1957.

156. Hawthorne, V. M., et al.: Tuberculosis in Man, Dog, and Cat, Brit. M. J. 2:675-678 (Sept. 21) 1957.

157. Grzybowski, S.: A Small Epidemic of Tuberculosis, Am. Rev. Tuberc. 65:432-441 (March) 1957.

158. Leonard, J. J.; Katz, S., and McCormick, G.: Recurrent Miliary Tuberculosis, New England J. Med. 256:435-441 (March 7) 1957.

159. Burke, R. M., and Weir, J. A.: Review of Cases of Nontuberculous Disease Originally

Diagnosed Pulmonary Tuberculosis, Am. Rev. Tuberc. 75:921-937 (June) 1957..

160. Schless, J. M., and Weir, J. A.: Nontuberculous Chest Cases Originally Diagnosed as Tuberculosis, U. S. Armed Forces M. J. 8:1261-1280 (Sept.) 1957.

161. Gray, J. A., and Spencer, G. E.: Study of 507 Patients Discharged from a Tuberculosis Service: A Year's Experience at a Naval Hospital, U. S. Armed Forces M. J. 8:1281-1290 (Sept.) 1957.

162. Allen, A. R.; Harmon, R. W.; Klacsan, L. J., and Stewart, K. M., Jr.: Accuracy of the Confirmatory Diagnosis of Tuberculosis, Am. J. Med. 22:904-914 (June) 1957.

163. Terry, R. B., and Gunnar, R. M.: Primary Miliary Tuberculosis of the Liver, J. A. M. A. 164:150-157 (May 11) 1957.

164. Walsh, J. J.; Linn, R. H., and Brancato, F.: Tuberculous Axillary Adenitis Following Application of P. P. D., Ann. Int. Med. 45:547-549 (Sept.) 1956.

165. Hirsch, J. G.; Schaedler, R. W.; Pierce, C. H., and Smith, I. M.: A Study Comparing the Effects of Bed Rest and Physical Activity on Recovery from Pulmonary Tuberculosis, Am. Rev. Tuberc. 75:359-409 (March) 1957.

166. Weir, J. A.; Taylor, R. L., and Fraser, R. S.: The Ambulatory Treatment of Patients Hospitalized with Pulmonary Tuberculosis, Ann. Int. Med. 47:762-773 (Oct.) 1957.

167. Frappier, A.; Desjardins, R., and Panisset, M.: Primary Resistance of Tubercle Bacilli to Streptomycin and Other Antituberculous Agents in the Province of Quebec, Canad. M. A. J. 76: 653-655 (April 15) 1957.

168. Bruce, L. G.; Cuthbert, J., and Ritchie, J. A.: Drug-Resistant Tubercle Bacilli in a Community, Scottish M. J. 2:83-87 (March) 1957.

169. Weiss, W.; Eisenberg, G. M., and Flippin, H. F.: Impact of Isoniazid on Tuberculous Meningitis, J. A. M. A. 164:947-951 (June 29) 1957.

170. Badger, T. C.: Treatment Failures in Tuberculosis, Ann. Int. Med. 47:794-800 (Oct.) 1957.

171. Amberson, J. B., et al.: Indications for Adjuvant Corticotropin and Corticosteroid Therapy in Tuberculosis: A Statement of the Committee on Therapy, Am. Rev. Tuberc. 76:708-710 (Oct.) 1957.

172. Why Have We Not Accepted BCG Vaccination? Report by the Medical Advisory Committee of Research Foundation, J. A. M. A. 164: 951-954 (June 29) 1957.

173. Dubos, R. J., et al.: Report of Ad Hoc Advisory Committee on BCG to the Surgeon General of the United States Public Health Service, Am. Rev. Tuberc. 76:726-731 (Nov.) 1957.

174. Wallgren, A. J.: BCG: Past, Present, and Future, Am. Rev. Tuberc. 76:726-731 (Nov.) 1957.

175. Pollock, T. M.: The Optimum Age for Mass B. C. G. Vaccination in England and Wales, Brit. M. J. 2:20-23 (July 6) 1957.

176. James, E. F.: Mass B. C. G. Vaccination, Correspondence, Brit. M. J. 2:712 (Sept. 21) 1957.

177. Myers, J. A.: A Summary of the Views Opposing BCG, Advances Tuberculosis Res. 8:272-303, 1957.

178. DeFriez, A. I., and Badger, T. L.: Tuberculosis in BCG Vaccinated Nurses: A Report of 5-Year's Experience at the Boston City Hospital, New England J. Med. 257:161-165 (July 25) 1957.

178a. Kendig, E. C.: BCG Vaccination in Virginia, J. Pediat. 51:54-57 (July) 1957.

179. Cortisone and Immunity in Tuberculosis, Annotations, Lancet 1:920 (May 4) 1957.

180. Prissick, F. H., and Masson, A. M.: Cervical Lymphadenitis in Children Caused by Chromogenic Mycobacteria, Canad. M. A. J. 75: 798-803 (Nov. 15) 1956.

181. Schmidt, L. H.; Huffmann, R., and Steenken, W.: The Pathogenicity of Atypical Chromogenic Mycobacteria for the Rhesus Monkey, Am. Rev. Tuberc. 75:169-179 (Feb.) 1957.

182. Wolinsky, E.; Smith, M. M.; Mitchell, R. S., and Steenken, W., Jr.: Atypical Chromogenic Mycobacteria Associated with Pulmonary Disease: Including a Report of 3 Cases, Am. Rev. Tuberc. 75:180-198 (Feb.) 1957.

183. Crow, H. E., et al.: A Limited Clinical, Pathologic, and Epidemologic Study of Patients with Pulmonary Lesions Associated with Atypical Acid-Fast Bacilli in the Sputum, Am. Rev. Tuberc. 75:199-222 (Feb.) 1957.

184. Siltzbach, L. E.: Progress in Sarcoidosis, Editorial, Am. J. Med. 22:841-847 (June) 1957.

185. Heller, S.; McLean, R. A.; Campbell, C. G., and Jones, I. H.: A Case of Coexistent Non-Meningitic Cryptococcosis and Boeck's Sarcoid, Am. J. Med. 22:986-994 (June) 1957.

186. Plummer, N. S.; Symmers, W. S. C., and Winner, H. I.: Sarcoidosis in Identical Twins with Torulosis as a Complication in One Case, Brit. M. J. 2:599-603 (Sept. 14) 1957.

187. Maycock, R. L.; Sullivan, R. D.; Greening, R. R., and Jones, R., Jr.: Sarcoidosis and Pregnancy, J. A. M. A. 164:158-163 (May 11) 1957.

188. MacCready, R. A.; Reardon, J. P., and Saphra, I.: Salmonellosis in Massachusetts: A 16-Year Experience, New England J. Med. 256:1121-1128 (June 13) 1957.

189. Saphra, I., and Winter, J. W.: Clinical Manifestations of Salmonellosis in Man: An Evaluation of 7779 Human Infections at the New York Salmonella Center, New England J. Med. 256:1128-1134 (June 13) 1957.

190. Hook, E. W.; Campbell, C. G.; Weens, H. S., and Cooper, G. R.: Salmonella Osteomyelitis in Patients with Sickle-Cell Anemia, New England J. Med. 257:403-407 (Aug. 29) 1957.

191. Thomas, M. E. M.: Enteritis from Tortoise, Foreign Letters (United Kingdom), J. A. M. A. 164:599 (June 1) 1957.

192. Watson, K. C.: The Relapse State in Typhoid Fever Treated with Chloramphenicol, Am. J. Trop. Med. 6:72-80 (Jan.) 1957.

193. Conroy, J. V.: Acute Ileitis with Ulceration and Perforation Due to Paratyphoid Fever—Report of 85 Cases, Mil. Med. 120:79-92 (Feb.) 1957.

194. Reimann, H. A., and Pang, T. L.: Chloramphenicol in Paratyphoid A: Observations with a Note on the Clinical Aspects of the Disease, A. M. A. Arch. Int. Med. 96:777-780 (Dec.) 1955.

195. O'Donnell, W. M., and Schrack, W. D.: Contaminated Milk: Clinical Aspects of the Paratyphoid "B" Epidemic in Lancaster County, Pennsylvania M. J. 60:483-485 (April) 1957.

196. Cvjetanovic, B. B.: Field Trials of Typhoid Vaccines, Am. J. Pub. Health 47:578-581 (May) 1957.

197. Spink, W. W.: The Significance of Bacterial Hypersensitivity in Human Brucellosis: Studies of Infection Due to Strain 19 Brucella Abortus, Ann. Int. Med. 47:871-874 (Nov.) 1957.

198. Wallis, H. R. E.: Brucellosis in Children, Brit. M. J. 1:617-621 (March 16) 1957.

199. Pfischner, W. C., Jr., et al.: Brucellosis in Egypt: A Review of Experience with 228 Patients, Am. J. Med. 22:915-929 (June) 1957.

200. Pinheiro, D.: Tetanus: General Considerations on 1,047 Cases Admitted to the Hospital Das Clinicas de São Paulo, J. Pediat. 51:171-180 (Aug.) 1957.

201. Garcia-Palmero, M. R., and Ramirez, R.: Generalized Tetanus: Analysis of 202 Cases, Ann. Int. Med. 47:721-730 (Oct.) 1957.

202. Dische, F. E., and Elek, S. D.: Experimental Food-Poisoning by Clostridium Welchii, Lancet 2:71-74 (July 13) 1957.

203. Moore, H. A., and Larsen, J. I.: Present Distribution of Diphtheria in the United States, Pub. Health Rep. 72:537-542 (June) 1957.

204. Detroit Diphtheria Experience of 1956, Editorials, Am. J. Pub. Health 47:751-752 (June) 1957.

205. Spivak, A. P.; Eisenberg, G. M.; Weiss, W., and Flippin, H. F.: Klebsiella Meningitis, Am. J. Med. 22:865-871 (June) 1957.

206. Brocklehurst, J. C.: Fatal Outbreak of Botulism Among Labrador Eskimos, Brit. M. J. 2:924 (Oct. 19) 1957.

207. Marshall, B. W., and Zimmerman, S. L.: Tularemic Pericarditis, A. M. A. Arch. Int. Med. 100:300-304 (Aug.) 1957.

208. Hughes, W. T., and Etteldorf, J. N.: Oropharyngeal Tularemia, J. Pediat. 51:363-372 (Oct.) 1957.

209. Atin, H. L., and Beetham, W. P.: Pasteurella Multocida Empyema: Report of a Case, New England J. Med. 256:979-981 (May 23) 1957.

210. Markley, K.; Gurmendi, G.; Chavez, P. M., and Bazan, A.: Fatal Pseudomonas Septicemias in Burned Patients, Ann. Surg. 145:175-181 (Feb.) 1957.

211. Prevatt, A. L., and Hunt, J. S.: Chronic Systemic Melioidosis: Review of Literature and Report of a Case with a Note on Visual Disturbance Due to Chloramphenicol, Am. J. Med. 23:810-823 (Nov.) 1957.

212. Rogers, L.: Thirty Year's Research on the Control of Cholera Epidemics, Brit. M. J. 2:1193-1197 (Nov. 23) 1957.

213. Finland, M., and Nichols, R. L.: Novobiocin, Antibiotica et Chemother. 4:209-392, 1957.

214. Cook, J., et al.: Staphylococcal Diarrhoea, with an Account of 2 Outbreaks in the Same Hospital, Brit. M. J. 1:542-547 (March 9) 1957.

215. Shooter, R. A.; Griffiths, J. D.; Cook, J., and Williams, R. E.: Outbreak of Staphylococcal Infection in a Surgical Ward, Brit. M. J. 1:433-436 (Feb. 23) 1957.

216. McDonald, S., and Timbury, M. C.: Unusual Outbreak of Staphylococcal Postoperative Wound Infection, Lancet 2:863-864 (Nov. 2) 1957.

217. Wysham, D. N., and Kirby, W. M. M.: Micrococcic (Staphylococcic) Infections in a General Hospital, J. A. M. A. 164:1733-1739 (Aug. 17) 1957.

218. Adams, R.: Prevention of Infection in Surgical Wounds, New England J. Med. 256:625-628 (April 4) 1957.

219. Turnbull, R. B., Jr.: Clinical Recognition of Postoperative Micrococcic (Staphylococcic) Enteritis, J. A. M. A. 164:756-761 (June 15) 1957.

220. Mathias, J. Q.; Shooter, R. A., and Williams, R. E. O.: Staphylococcus Aureus in the Feces of Hospital Patients, Lancet 1:1172-1173 (June 8) 1957.

221. Gould, J. C., and Cruikshank, J. D.: Staphylococcal Infection in General Practice, Lancet 2:1157-1161 (Dec. 7) 1957.

222. Ravenholt, R. T.; Wright, P., and Mulhern, M.: Epidemiology and Prevention of Nursery-Derived Staphylococcal Disease, New England J. Med. 257:789-795 (Oct. 24) 1957.

223. Wysham, D. N., et al.: Staphylococcal Infections in an Obstetric Unit: I. Epidemiologic Studies of Pyoderma Neonatorum, New England J. Med. 257:295-303 (Aug. 15) 1957; II. Epidemiologic Studies of Puerperal Mastitis, New England J. Med. 257:304-306 (Aug. 15) 1957.

224. Shirger, A.; Martin, W. J., and Nichols, D. R.: Micrococcal Bacteremia Without Endocarditis: Clinical Data and Therapeutic Considerations in 109 Cases, Ann. Int. Med. 47:39-48 (July) 1957.

225. Melton, J. T., and Logue, B.: Treatment of Staphylococcic Endocarditis: Report of 7 Cases, A. M. A. Arch. Int. Med. 99:581-586 (April) 1957.

226. Dowling, H. F., et al.: The Clinical Use of Antibiotics in Combination, Editorials, A. M. A. Arch. Int. Med. 99:536-538 (April) 1957.

227. Rahman, A. N., and Bennett, I. V.: The Rate of Penicillin's Bactericidal Action on Staphylococci in Vitro: Some Observations on the So-Called Zone Phenomenon, Bull. Johns Hopkins Hosp. 100:17-27 (Jan.) 1957.

228. Petersdorf, R. G.; Bennett, I. V., and Rose, M. C.: The Sensitivity of Pathogenic Bacteria to a Series of Antibiotics, Bull. Johns Hopkins Hosp. 100:1-13 (Jan.) 1957.

229. Garrod, L. P.: The Erythromycin Group of Antibiotics, Brit. M. J. 2:57-63 (July 13) 1957.

230. Finland, M.: Staphylococci, Antibiotics, and Endocarditis, Editorial, Circulation 15:641-645 (May) 1957.

231. Halbert, S. P.; Kazar, C. S., and Sevick, L.: Mixed Bacterial Infections in Relation to Antibiotic Activities: II. The Role of Staphylococcal Antibiotic in a Clostridium Septicum Staphylococcus Albus Infection, Antibiotics & Chemother. 7:235-242 (May) 1957.

232. Reimann, H. A.: Transformation and Culture Phase Dissociation of Staphylococcus (Micrococcus Pyogenes), Proc. Soc. Exper. Biol. & Med. 96:411-417 (Nov.) 1957.

233. LaBoccetta, A. C.; Rosenberg, M.; Harris, S., and Harris, T. N.: Scarlet Fever: Results of a Controlled Study of 609 Patients Treated with Penicillin and Sulfisoxazole, Am. J. Med. 22:458-468 (March) 1957.

234. Morris, A. J., and Rammelkamp, C. H., Jr.: Benzathine Penicillin G in the Prevention of Streptococcic Infections, J. A. M. A. 165:664-667 (Oct. 12) 1957.

235. Sherwood, R. W.; Gronbeck, C., and Denny, F. W., Jr.: Reactions from Multiple Injections of Benzathine Penicillin G, J. A. M. A. 165:667-671 (Oct. 12) 1957.

236. Denny, F. W.; Perry, W. D., and Wannamaker, L. W.: Type-Specific Streptococcal Antibody, J. Clin. Invest. 36:1092-1100 (July) 1957.

237. Ross, R. S.; McKusick, V. A., and Harvey, J. C.: The Problem of Fever in Patients with Valvular Heart Disease, J. A. M. A. 165:1-7 (Sept. 7) 1957.

238. Denton, C., et al.: Bacterial Endocarditis Following Cardiac Surgery, Circulation 15:525-531 (April) 1957.

239. Santos-Buch, C. A.; Koenig, M. G., and Rogers, D. E.: Oral Treatment of Subacute Bacterial Endocarditis with Phenoxymethyl Penicillin (Penicillin V), New England J. Med. 257:249-257 (Aug. 8) 1957.

240. Kellow, W. F., and Dowling, H. F.: Current Concepts in the Management of Bacterial Endocarditis, A. M. A. Arch. Int. Med. 100:322-330 (Aug.) 1957.

241. Jones, W. F., and Finland, M.: Susceptibility of Enterococcus to 11 Antibiotics in Vitro with Especial Reference to Species Differences, Am. J. Clin. Path. 27:467-481 (April) 1957.

242. Antibiotics and Sore Throat, Leading Articles, Lancet 1:1128-1130 (June 1) 1957.

243. Rheumatic Fever, Foreign Letters (Sweden), J. A. M. A. 164:1145-1146 (July 6) 1957.

244. Heart Association Issues Revised Statement on Prevention of Rheumatic Fever, News and Comment, A. M. A. J. Dis. Child. 93:465 (April) 1957.

245. Wood, H. F., et al.: A Controlled Study of 3 Methods of Prophylaxis Against Streptococcal Infection in a Population of Rheumatic Children: I. Streptococcal Infections and Recurrences of Acute Rheumatic Fever in the First 2 Years of the Study, New England J. Med. 257:394-398 (Aug. 29) 1957.

246. Dock, D. S., and Guze, L. B.: Subacute Bacterial Endocarditis Occurring in a Patient Receiving Oral Penicillin as Prophylaxis Against Rheumatic Fever, Ann. Int. Med. 47:577-581 (Sept.) 1957.

247. Illingworth, R. S.; Lorber, J.; Holt, K. S., and Rendle-Short, J.: Acute Rheumatic Fever in Children: A Comparison of 6 Forms of Treatment in 200 Cases, Lancet 2:653-659 (Oct. 5) 1957.

248. Duman, L. J.; Githens, J. H., and Hoffman, M. S.: Role of Bed Rest in Treatment of Rheumatic Fever: Review of Literature and Survey of Current Opinions, J. A. M. A. 164:1435-1438 (July 27) 1957.

249. Petersdorf, R. G., et al.: Pneumococcal Pneumonia Treated with Penicillin and Aspirin, Bull. Johns Hopkins Hosp. 101:1-12 (July) 1957.

250. Austrian, R.: Current Status of Therapy in the Pneumonias, J. A. M. A. 163:1040-1045 (March 23) 1957.

251. Jones, W. F., and Finland, M.: Susceptibility of Pneumococci to 11 Antibiotics in Vitro, Am. J. M. Sc. 233:312-319 (March) 1957.

252. Austrian, R.: Pneumococcal Endocarditis, Meningitis, and Rupture of the Aortic Valve, A. M. A. Arch. Int. Med. 99:539-544 (April) 1957.

253. Shirger, A.; Martin, W. J.; Morlock, C. G., and Baggenstoss, A. H.: Bacteremia Due to Diplococcus Pneumoniae Associated with Disease

of the Biliary Tract, A. M. A. Arch. Int. Med. 99:622-627 (April) 1957.

254. Oral Penicillin in the Treatment of Gonorrhea, Annotations, Brit. M. J. 2:518 (Aug. 31) 1957.

255. Marmel, M., and Prigot, A.: Oral Penicillin G Combined with Probenecid in the Treatment of Gonorrhea in the Male, Am. J. M. Sc. 233:256-258 (March) 1957.

256. Thayer, J. D.; Perry, M. I.; Magnuson, H. J., and Garson, W.: Failure of Penicillin to Kill Phagocytized Neisseria Gonorrhoeae in Tissue Culture, Antibiotics & Chemother. 7:311-314 (June) 1957.

257. Young, R. V.; Cleve, E. A., and Vincente-Mastellari, A.: Acute Pulmonary Histoplasmosis on the Isthmus of Panama, A. M. A. Arch. Int. Med. 100:430-435 (Sept.) 1957.

258. Spencer, G. E., and Gray, J. A. C.: The Problem of Histoplasmosis in a Military Tuberculosis Hospital, Am. Rev. Tuberc. 75:833-835 (May) 1957.

259. Packard, J. S.; Finkelstein, H., and Turner, W. E.: Acute Pulmonary Histoplasmosis: Treatment with Cortisone, A. M. A. Arch. Int. Med. 99:370-375 (March) 1957.

260. Sutliffe, W. D.: Experience with the Course and Chemotherapy of Chronic Pulmonary Histoplasmosis, Am. Rev. Tuberc. 75:912-920 (June) 1957.

261. Chapman, M. G., and Kaplan, L.: Cardiac Involvement in Coccidioidomycosis, Am. J. Med. 33:87-98 (July) 1957.

262. Keye, J. D., and Magee, W. E.: Fungal Diseases in a General Hospital: A Study of 88 Patients, Am. J. Clin. Path. 26:1235-1253 (Nov.) 1956.

263. Baker, R. D.: Mucormycosis—a New Disease? J. A. M. A. 163:805-808 (March 9) 1957.

264. Harris, J. S., et al.: North American Blastomycosis in an Epidemic Area, Pub. Health Rep. 72:95-100 (Feb.) 1957.

265. Gentles, J. C.: Athlete's Foot Fungi on Floors of Communal Bathing-Places, Brit. M. J. 1:746-748 (March 30) 1957.

266. Lombardo, T. A.; Rabson, A. S., and Dodge, H. T.: Mycotic Endocarditis: Report of a Case Due to Cryptococcus Neoformans, Am. J. Med. 22:664-670 (April) 1957.

267. Reed, R. W., and Kalz, G.: The Human Leptospiroses, Am. J. M. Sc. 233:320-333 (March) 1957.

268. Murphy, L. C., and Alexander, A. D.: Significance of the Leptospires in Military Medicine, Mil. Med. 121:1-11 (July) 1957.

269. Broome, J. C., and Norris, T. S.: Failure of Prophylactic Oral Penicillin to Inhibit a Human Laboratory Case of Leptospirosis, Lancet 1:721 (April 6) 1957.

270. Coghlan, J. D.; Norval, J., and Seiler, H. E.: Canicola Fever in Man Through Contact with Infected Pigs, Brit. M. J. 1:257-261 (Feb. 2) 1957.

271. Bossak, H. N.; Falcone, V. H., and Harris, A.: A Year's Experience with a Nationwide TPI Testing Service, Pub. Health Rep. 72:317-320 (April) 1957.

272. Fiumara, N. J., and Hill, W.: Congenital Syphilis in the Absence of Positive Serology in the Mother: A Third Indication for the Treponema Pallidum Immobilization Test, J. A. M. A. 163: 1037-1039 (March 23) 1957.

273. Rein, C. R., and Kelcec, L. C.: Biologically False-Positive Serologic Reactions, Editorials, J. A. M. A. 163:1046-1047 (March 23) 1957.

274. Packer, H.: Minor Venereal Diseases in the United States, Pub. Health Rep. 72:363-366 (April) 1957.

275. Disseminated Sclerosis, Leading Articles, Brit. M. J. 1:1228-1229 (May 25) 1957.

276. Ichelson, R. R.: Cultivation of Spirochaetes from Spinal Fluids of Multiple Sclerosis Cases and Negative Controls, Proc. Soc. Exper. Biol. & Med. 95:57-58 (May) 1957.

277. Herrell, W. E.: Infectious Diseases, Cortisone and Related Steroids, Antibiotic Med. & Clin. Ther. 4:297-304 (May) 1957.

278. Chang, T. W., and Weinstein, L.: Effect of Cortisone on Treatment of Tetanus with Antitoxin, Proc. Soc. Exper. Biol. & Med. 94:431-433 (March) 1957.

279. Bowen, S. T.; Gowen, J. W., and Tauber, O. E.: Cortisone and Mortality in Mouse Typhoid: I. Effect of Hormone Dosage and Time of Injection, Proc. Soc. Exper. Biol. & Med. 94:476-479 (March) 1957; II. Effect of Natural and Acquired Immunity, Proc. Soc. Exper. Biol. & Med. 94: 482-485 (March) 1957.

280. Allenby, K. D.: Deaths Associated with Steroid-Hormone Therapy, Lancet 1:1104-1110 (June 1) 1957.

281. Mills, L. C.; Boylston, B. F.; Greene, J. A., and Moyer, J. H.: Septic Arthritis as a Complication of Orally Given Steroid Therapy, J. A. M. A. 164:1310-1314 (July 20) 1957.

282. Brailley, A. G., and Husebye, K.: Varicella Pneumonia with Prolonged Roentgenologic Changes, in Proceedings of the Minnesota Society of Internal Medicine, Oct. 21, 1957, p. 4.

283. Gale, D., and Lord, J. D.: Overgrowth of Serratia Marescens in Respiratory Tract, Simulating Hemoptysis: Report of a Case, J. A. M. A. 164:1328-1330 (July 20) 1957.

284. Truelove, L. H.: Enhancement of Mantoux Reaction Coincident with Treatment with Cortisone and Prednisolone, Brit. M. J. 2:1135-1137 (Nov. 16) 1957.

285. Chase, G. O.: Death Due to Eosinophilic Myocarditis Related to Trichinosis: Report of a Case, J. A. M. A. 165:1826-1829 (Dec. 7) 1957.

286. Markell, E. K., and Lewis, W. P.: Effect of Cortisone Treatment on Immunity to Subsequent Reinfection with Trichinella in the Rat, Am. J. Trop. Med. 6:553-561 (May) 1957.

287. Guze, L. B., and Beeson, P. B.: Observations on the Reliability and Safety of Bladder Catheterization for Bacteriologic Study of the Urine, New England J. Med. 255:474-475 (Sept. 6) 1956.

288. Kass, E. H.: Bacteriuria and the Diagnosis of Infections of the Urinary Tract, with Observations on the Use of Methionine as a Urinary Antiseptic, A. M. A. Arch. Int. Med. 100:709-714 (Nov.) 1957.

289. Kass, E. H., and Schneiderman, L. J.: Entry of Bacteria into the Urinary Tracts of Patients with Inlying Catheters, New England J. Med. 256:516-557 (March 21) 1957.

290. Lunt, R. L.; Dutton, W. A.; Dewhurst, C. J., and Russell, C. S.: The Incidence of Infection Following Gynaecological Operations, Lancet 1:1240-1243 (June 15) 1957.

291. Harris, H. J.: Postoperative Urinary Tract Infections, Correspondence, J. A. M. A. 165:2220 (Dec. 28) 1957.

292. Clabaugh, J. G., and Rhoads, P. S.: Efficacy of Urethral Catheterization for Determination of Urinary Tract Infection: Results with a New Technique, J. A. M. A. 165:815-818 (Oct. 19) 1957.

293. Dalgaard, J. B.: Family Epidemic of Ornithosis with Interhuman Transmission, Tidsskr. norske lægerfor. 77:47-50 (Jan. 15) 1957.

294. Kemmerer, G.; Haussmann, H. G.; Schoop, G., and Kauker, E.: Clinical Observations and Epidemiology of Human Ornithosis Transmitted by Pigeons, German M. Month. 2:7-9 (Jan.) 1957.

295. Cawley, E. P., and Wheeler, C. E.: Rocky Mountain Spotted Fever, J. A. M. A. 163:1003-1007 (March 23) 1957.

296. Dedrick, J. W.: Listeria Meningitis, a Report of 8 Cases, Am. J. M. Sc. 233:617-621 (June) 1957.

297. Edmunds, P. N.; Nicholson, D. N., and Douglas, D. M.: Two Cases of Listerial Meningitis in Infants, Brit. M. J. 2:188-191 (July 27) 1957.

298. Korn, R. J.; Yakulis, V. J.; Lemke, C. E., and Chomet, B.: Cold Agglutinins in Listeria Monocytogenes Infections, A. M. A. Arch. Int. Med. 99:573-580 (April) 1957.

299. Berg, R.; Weinberger, H., and Dienes, L.: Acute Hemorrhagic Cystitis: An Infection Associated with Pleuropneumonia-like Organisms and Related to Urethritis and Prostatitis, Am. J. Med. 22:848-864 (June) 1957.

300. Kean, B. H.: The Nature of Diffuse Amebic Hepatitis, Editorial, Am. J. Digest. Dis. 2:342-347 (June) 1957.

301. Manson-Bahr, P., and Muggleton, W. J.: Rectal Biopsy as an Aid to the Diagnosis of Amoebic Dysentary and Allied Diseases of the Colon, Lancet 1:763-765 (April 13) 1957.

302. Diaz-Rivera, R. S., et al.: The Pathogenesis of Manson's Schistosomiasis, Ann. Int. Med. 47:1082-1107 (Dec.) 1957.

303. Stillerman, M.: Mild Neonatal Toxoplasmosis: Case Report with a 4-Year Serologic and Dermal Sensitivity Study, A. M. A. J. Dis. Child. 93:563-567 (May) 1957.

304. Jacobs, L., and Lunde, M. N.: Hemagglutination Test for Toxoplasmosis, Science 125: 1035 (May 24) 1957.

305. McGill, R. J., and Goodbody, R. A.: Sarcosporidiosis in Man with Periarteritis Nodosa, Brit. M. J. 2:333-334 (Aug. 10) 1957.

306. Webster, B. H.: Human Isosporosis: A Report of Three Cases with Necropsy Findings of One Case, Am. J. Trop. Med. 6:86-89 (Jan.) 1957.

307. Gajdusek, D. C.: Pneumocystis Carinii: Etiologic Agent of Interstitial Plasma Cell Pneumonia of Premature and Young Infants, Pediatrics 19:543-565 (April) 1957.

308. Birch, C. L., and Anast, B. P.: The Changing Distribution of Helminthic Diseases in the United States, J. A. M. A. 164:121-126 (May 11) 1957.

309. White, J. C.; Sweet, W. H., and Richardson, E. P.: Cysticercosis Cerebri: A Diagnostic and Therapeutic Problem of Increasing Importance, New England J. Med. 256:479-486 (March 14) 1957.

310. Arseni, C.: Cysticercosis of the Brain, Brit. M. J. 2:494-497 (Aug. 31) 1957.

311. Swartzwelder, J. C., et al.: Dithiazanine, an Effective Broad-Spectrum Anthelmintic: Results of Therapy of Trichuriasis, Strongyloidiasis, Enterobiasis, Ascariasis, and Hookworm Infection, J. A. M. A. 165:2063-2067 (Dec. 21) 1957.

312. Chandler, A. C.: Interrelations Between Nutrition and Infectious Disease in the Tropics, Am. J. Trop. Med. 6:195-208 (March) 1957.

313. Bond, V. P.: The Role of Infection in Illness Following Exposure to Acute Total Body Irradiations, Bull. New York Acad. Med. 33: 369-374 (May) 1957.

314. Blattner, R. J.: Severe Infections in Splenectomized Infants and Children, Comments on Current Literature, J. Pediat. 51:223-225 (Aug.) 1957.

315. Martin, C. M.; Waite, J. B., and McCullough, N. B.: Antibody Protein Synthesis by Lymph Nodes Homotransplanted to a Hypogamma-

globinic Adult, J. Clin. Invest. 36:405-421 (March) 1957.

316. Donhauser, J. L.: Primary Acute Mesenteric Lymphadenitis: A Review of 198 Cases, A. M. A. Arch. Surg. 74:528-535 (April) 1957.

317. Louttit, R. T. S.: Treatment of Acute Appendicitis, Correspondence, Brit. M. J. 1:883 (April 13) 1957.

318. Prolonged Antibiotic Treatment of Severe Bronchiectasis: A Report by a Subcommittee of the Antibiotics Clinical Trials (Non-Tuberculous) Committee of the Medical Research Council, Brit. M. J. 2:255-259 (Aug. 3) 1957.

319. Dygert, H. P.: Snuff—a Source of Pathogenic Bacteria in Chronic Bronchitis, New England J. Med. 257:311-313 (Aug. 15) 1957.

320. Kelly, C. D., and Layne, S.: Bacteria Found in the Air Over the Atlantic Ocean, Canad. J. Microbiol. 3:457-460 (April) 1957.

321. Gordon, J. E., and Ingalls, T. H.: Contact and Air-Borne Transmission of Infectious Agents, Am. J. M. Sc. 233:334-357 (March) 1957.

322. Innes, J. R. M.: The Nature and Variety of Diseases of Laboratory Animals and Their Significance to Medical Research, Bull. New York Acad. Med. 33:807-810 (Nov.) 1957.

323. Crossland, P. M.: Dermatological Radiation Therapy in This Nuclear Age—an Appraisal, J. A. M. A. 165:647-650 (Oct. 12) 1957.

324. Meyer, K. F.: Some Observations on Infective Diseases in Russia, Am. J. Pub. Health 47:1083-1092 (Sept.) 1957.

Iron

Metabolism, Biochemistry, and Clinical Pathological Physiology—Review of Recent Literature

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In general biology, iron plays an irreplaceable role as a catalyzer. It is found in every living species, but its proportion increases as evolution progresses in the animal kingdom.

The oligoelement has many virtues, one of them being a growth-promoting capacity. A culture of beer yeast in an iron-free medium presents only a poor development; the same phenomenon is observed on many other organisms.

The biocatalyzing property has been known since Warburg demonstrated the transportation of oxygen by the metal. Iron is found in cellular ferments, where it edifies ferric porphyrins, the most famous example of which is hemoglobin. Within these enzymes it keeps its variable valency Fe^{++} and Fe^{+++} that enables it to transfer ions and to participate in oxidoreduction processes; thus iron bestows their activity to the cytochromes, peroxidases, catalase, and cytochrome oxidase, Warburg's yellow ferment. Cellular life would be impossible without iron.

The erythropoietic property will be described later.

The human body contains 3 to 5 gm. of iron, a proportion of 50 to 60 mg. per kilogram of body weight.

Two-thirds is incorporated in hemoglobin. This pigment contains 3.34 parts of iron per thousand; 25 mg. of the metal is set free daily by physiological hemolysis but is immediately taken up by the continuous erythropoietic process.

One-fifth constitutes the iron store, chiefly accumulated in the liver, the spleen, and the bone marrow. A part of this reserve lends itself very easily to the elaboration of red blood corpuscles; it is called the "labile iron pool" and has been estimated at 133 mg.[126,379]

The remainder is "parenchymatous iron," divided between myoglobin (7%) and enzymatic iron.

It should be noted that, like all other biological compounds, iron combinations are continuously destroyed and renewed. Hemoglobin, however, makes an exception to this rule, since it remains stable within the erythrocyte. This peculiarity allows the evaluation of the life span of red blood corpuscles by means of iron or nitrogen isotopes.

A normal adult needs between 3 and 15 mg. of iron per day,[116] a child under 12 years, between 7 and 12 mg. In the second half of pregnancy, 15 mg. should be a minimum, just as during lactation; the same quantity is indicated for adolescents from 14 to 20 years.

A usual day's food procures 10 to 40 mg. of the metal. The major part of it makes a simple transit through the digestive system without being absorbed. Iron contained in green vegetables is very easily assimilated (spinach and cabbage, especially); this is also true for other nutriments, such as sauerkraut, whole bread, egg yolk, carrots, and certain fruits. Nevertheless, the worth of alimentary products as iron suppliers does not depend on their richness but on the facility with which they cede it during digestion.[149]

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Digestive Absorption of Iron

The assimilation of iron takes place principally in the stomach and in the small intestine, with a decreasing intensity from pylorus to colon.

The degree of absorption is conditioned by the needs of the organism. After an acute blood loss or in the case of iron deficiency, the resorption curve rises sharply. Investigations made in those circumstances with iron isotopes show that four hours after their ingestion "marked" atoms may already be found in circulating erythrocytes.[135] Practically, however, the administration of iron by mouth allows an appreciable synthesis of hemoglobin only after three to five days.

A normal dog absorbs between 1.6% and 6% of the radioactive iron given by mouth. In deficiency states, this proportion may reach 66%.[341] According to Heilmeyer, we resorb in usual circumstances 20% of our alimentary iron.

The serum iron level has no direct influence on the intestinal absorption of the metal. During a continuous infusion of iron, isotopes of this metal given per os are absorbed as well by a normal animal as in case of deficiency.

Iron passes the intestinal mucosa only if bivalent, at least in the human being. Dogs and rats, on the contrary, assimilate ferric as well as ferrous ions. The gastric content has an extraordinary reducing power, efficient on low pH. Even when the iron is isolated, the stomach wall absorbs important quantities of it.[341]

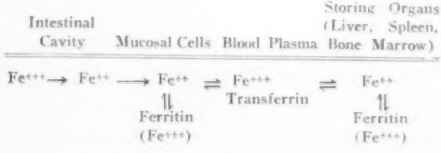
It has been demonstrated in vitro that alimentary iron is already split off by HCl alone. The scission is enhanced by addition of pepsin; the totality of the metal is, however, never separated.[335]

The principal element in reducing iron to bivalency is ascorbic acid (vitamin C), which also possesses the property of exciting the gastric secretion [147,365]; its therapeutic value is therefore outstanding. Bile, too, has power to set the alimentary iron free, though it acts in neutral or slightly alkaline media. Its effect equals less than half that of the gastric juice.

Recently, Stern et al.[339] showed the influence of the intestinal flora. By administration of oxytetracycline to rabbits, they reduce the flora to mere Proteus vulgaris; no more iron is absorbed, and the serum iron curve is flat even if the animals are prepared by an important blood-letting. When these rabbits subsequently receive enterococci and Escherichia coli resistant to oxytetracycline, the oral doses of iron pass immediately into the circulation.

The regulation of iron absorption seems to be a part of the functions of the intestine itself. Granick established that the cells of the digestive mucosa contain a special protein called *apoferritin*. Trivalent iron combines itself to this protein to form *ferritin;* their union is reversible and takes place only through the medium of an enzyme; in vitro, for instance, it requires the presence of ground liver.

The introduction of iron into intestinal cells provokes the formation of apoferritin; this synthesis seems to be possible only to a limited extent. When saturation is achieved, no more metal can be accepted until ferritin abandons iron to blood plasma. Granick called this the *mucosal block*. His scheme illustrating this mechanism is well known:



The transit of iron through the intestinal mucosa depends consequently on the velocity of the oxidation of bivalent iron to form ferritin (Fe^{+++}) and on its subsequent reduction, indispensable to be carried by the blood stream. A digestive hypoxia (caused by anemia, for example) could favor the oxidoreduction potential of the digestive cells in that way.

The efficiency of the mucosal block is however not complete:

1. Every protracted anemia, even if not due to deficiency of iron (pernicious, aplastic, or hemolytic anemias), may be accompanied by an exaggerated assimilation of iron from the intestine. This fact has been well demonstrated in cases of phenylhydrazine anemia.[178]

2. An exclusive wheat diet given to rats and severe protein restrictions in men also bring forth a failure of the mucosal block, exaggerating the resorption of iron. Tissue hemosiderosis may be the result.

Nevertheless, in ordinary circumstances the mucosal block constitutes an efficient mechanism of protection against an excessive iron intake. In a general way, the absorption will be proportional to the needs and will consequently act according to the importance of the iron stores.

Certain circumstances oppose themselves against the absorption of iron:

1. A high digestive pH promotes the formation of alkaline insoluble iron compounds.

2. Phytates and phosphates make nonionized precipitates with iron.

3. The absence of free HCl is another obstacle. The acid ionizes iron and solubilizes it. Its role is not primordial, as bile and intestinal flora may replace it at least partially. This is the reason why achylia does not provoke an iron deficiency by itself.

The Deposit of Iron in the Organism

Iron stores are accumulated in the whole of the reticuloendothelial system, especially in the liver, the spleen, and the bone marrow. The establishment of these reserves begins in utero, where they come from the maternal blood. They are composed of (1) monomolecular ferrous and ferric compounds, (2) ferritin, and (3) hemosiderin.

Ferritin.—This substance is composed of colloidal apoferritin containing in a sol complex iron micelles that do not precipitate and thus remain available to erythropoiesis. Ferritin is the richest in iron of all normal biological compounds. Chemically it belongs to the γ_1-globulins, with a molecular weight of 465,000. Neither nucleoproteids nor phosphor enter into its composition.[266] The acquisition of ferritin in the stock organs happens exactly as in the intestinal mucosa cells. Free apoferritin does not exist in tissues; it appears only at the moment of introduction of iron. Its cellular concentration changes according to offer and demand of iron.[101,309] The liver and the spleen are particularly rich in ferritin; it may be salted out of aqueous extracts of these tissues by cadmium sulfate.

Entirely separated from iron metabolism is another property of ferritin: It intervenes in irreversible shock, hypertension, and antidiuresis. It has been demonstrated that ferritin and the vasodepressive substance of the liver (VDM) are identical. It inhibits the vasoconstrictive action of epinephrine and exerts an experimental antidiuretic effect on dogs and rabbits, mediated through the posterior hypophysis.[18] Normally it is never present in blood serum, but it may invade the blood stream in great quantities in certain experimental and pathological circumstances—decompensated hepatic cirrhosis, nephrotic syndrome, and heart failure. According to Klucharev, however, the depressive action of ferritin injected intravenously is not very great.

Hemosiderin.—This compound is built when the available quantity of proteins and/or the excess of iron do not allow any more synthesis of ferritin. Hemosiderin contains, indeed, more iron and less protein. Its relation to ferritin is poorly known; it could be a condensation of several molecules of ferritin.[100,385] The following differences exist between both compounds: Ferritin is soluble in water; hemosiderin is not. Ferritin iron is masked for all histological techniques; hemosiderin iron can be disclosed by Perls' or Turnbull's reactions. Ferritin contains between 9% and 24% iron in sol form, hemosiderin, between 29% and 36% as a gel. This explains why hemosiderin is hardly mobilized

and therefore mostly unavailable for the normal iron metabolism, and yet it may disappear from animal tissues after repeated bleeding.

In general, the amount of iron deposited in different organs parallels their richness in reticuloendothelial tissue. The reticuloendothelial system intervenes in two ways: (1) by phagocytosis of erythrocytes (they retain a part of the hemoglobin iron and release bilirubin); (2) by athrocytosis of the colloidal iron transportated by the blood plasma.

The normal stores of the human body suffice to repair a hemorrhage of about 2 liters.

The Transport of Iron

Serum iron as it is given is a transport iron. It stays but a little time in the blood, where its form is trivalent.

It has long been known that the blood serum iron is not dialyzable but that it becomes so after acidification to pH 4.5 at least.[378] More recently it has been shown that ferric ions are bound to a specific plasma protein. It is one of the β_1-globulins, contained in Cohn's Fraction IV-7. This has been confirmed by Wallenius by combined electrophoresis and autoradiography of the plasma from dogs that had received radioactive iron; the metal was always found in the company of β-globulins. The same result is obtained when mixing iron isotopes with serum in vitro. These experiments refute Thedering's hypothesis, according to which peroral iron is bound to albumin, while parenteral iron combines with globulins.

The transport protein, called *transferrin* in Scandinavia and *siderophilin* in Anglo-American literature, is a pseudoglobulin with a molecular weight of approximately 90,000. It amounts to 3% of total plasma proteins, i. e., a level of 0.25 gm. %. Its physicochemical behavior is that of an albumin or an α-globulin (in salt precipitation, for example). Each of its molecules may contain two atoms of iron, the metal being always trivalent and ionized. According to Laurell, the reaction would be as follows:

$$2Fe^{+++} + 2HCO_3 + \text{transferrin} \rightleftharpoons 4H^+ + [(FeOH.CO_3)\,(\text{transferrin} - 4H^+)]$$

In vitro, siderophilin combines with copper and zinc too. The substitution of one metal for the other is easily effected by changes of the pH values of the solutions. Iron and copper form with the protein complexes having specific absorption spectra.[349] In vivo, siderophilin only carries iron, ceruloplasmin serving as a vehicle for copper.[162] It accepts free iron from intestinal cells, iron stores, and blood-destroying organs and conveys it to the bone marrow and to other viscera.

In physiological circumstances, transferrin is not completely loaded with iron but only to the amount of one-third. The normal total saturation, called *total iron binding capacity*, is evaluated at 300μg. of iron per 100 cu. cm.[39,85,132,207,246,284,367,397] It expresses the quantity of siderophilin in circulation. There is no sexual difference.[284] The complete saturation calls for 1.25×10^{-3} mg. of iron per milligram of the protein. The free fraction of transferrin, *unsaturated iron-binding capacity*, amounts to nearly 200μg. %. The *saturation coefficient* $\left(\frac{\text{serum iron}}{\text{total iron-binding capacity}}\right)$ expresses the degree of saturation. Its normal value is of about one-third: 33%,[132] 34%,[284] $35 \pm 6.4\%$.[397]

Variations of the Transferrin Level.—1. The serum content of transferrin changes in a way opposite to that of serum iron. A low sideremia is accompanied by a high total iron-binding capacity, for example, in iron deficiency. During pregnancy its level rises from the sixth month on and falls to a normal value immediately after delivery.[207] Inversely, a high serum iron level is concomitant with a low blood transferrin concentration. This phenomenon, encountered in pernicious anemia, disappears during specific treatment.[161,374]

2. In acute hepatitis, notwithstanding a considerable elevation of circulating iron,

the siderophilin increases notably [161]; in liver cirrhosis it is often low.

3. Every inflammation and malignant tumor, as well as uremia, provokes a fall in transferrin concentration. As the sideremia is still more reduced, the saturation coefficient also decreases.

4. In aplastic anemias, the quantity of transferrin is inferior to normal.[132,367]

5. This is also the case in deficiency dysproteinemias [366]; every trouble of protein metabolism may be reflected in the synthesis of siderophilin.

It appears completely impossible to create in vivo a sideremia that exceeds the total saturation of transferrin. This *braking effect* was discovered by Waldenström; injecting great amounts of ionized iron, he was unable to obtain the serum iron level as calculated theoretically from the plasma volume and the quantity of the injected metal. The elevation of ferriemia was always blocked at a maximum that corresponded to the total iron-binding capacity. The excess of iron immediately leaves the blood stream to form extravascular complexes.[147,256] At this moment precisely occur the symptoms of intravenous iron poisoning. They are due to the injury to the capillaries and possibly to the irritation of the central nervous system; the symptoms are redness of the face, sneezing, nausea and vomiting, headache, and sometimes even serious shock.

Colloidal nonionized iron, on the contrary, is well tolerated, for it releases its iron slowly. Intravenous iron saccharate behaves as a foreign body and is captured by the reticuloendothelial system, where the metal is set free gradually. Once ionized, these atoms combine themselves immediately with transferrin.

Like Laurell, Heilmeyer [147] believes that the intestinal absorption of iron is influenced by the saturation coefficient of siderophilin. A great need in iron (deficiency or pregnancy) produces a diminution of the sideremia and a rise of transferrin level, i. e., a fall of the saturation coefficient. At the same time, the absorption becomes more intense. On the contrary, if the iron stores are important, the coefficient climbs up and the absorption slackens or even stops.

At any rate, the intervention of this coefficient in the celerity of the evacuation of iron from intestinal cells is surely limited. Finch et al.,[100] nourishing animals with diets permitting an excessive iron resorption, observed a total saturation of transferrin in two weeks. The digestive absorption remains nevertheless important for several weeks. Moore, et al.[247] made dogs deficient in iron by repeated and measured blood-letting. They then replaced the total lost metal by one single intravenous injection; if they subsequently administered some radioactive iron per os, they found it to be absorbed as intensely as if the entire deficiency still existed; the absorption abated only after seven or eight days. Intravenous injections of β_1-globulin raise the total iron-binding capacity and lower the saturation coefficient but are unable to change the digestive absorption.[392] Nephrotic patients have a low serum iron and a low transferrin concentration, although its saturation is nearly complete; iron is, however, conveniently absorbed. In hemochromatosis, finally, there also exists a very rapid absorption of iron in spite of a saturation often of about 100%.

Transferrin may be measured according to two principles:

1. In vivo, the slow injection of 10 mg. of ionized iron (sulfate or citrate) provokes slight symptoms of intoxication. The iron exceeding the total iron-binding capacity will have left the blood stream within five minutes. The siderophilin is completely saturated at that moment, and the extemporaneous estimation of serum iron corresponds to the total iron-binding capacity.

2. Schade and Caroline [307] showed that the addition of iron to a solution of transferrin produces the appearance of a typical salmon rose color. Beyond complete saturation this color does not increase; its absorp-

tion spectrum is well defined with a maximum at 560 millimicrons. That principle is adapted in the dosage in vitro.[161, 207,284,397]

The Excretion of Iron

Even in pathological situations iron is practically not excreted.

In the feces, the metal does not exceed the quantity furnished by alimentation. Using iron isotopes, Hahn[136] could demonstrate that the loss of iron through the digestive tract is trifling, averaging 0.05 to 0.4 mg. a day. It has its origin exclusively in the cellular desquamation.

A little portion of iron is eliminated through the bile, but it is minimal even in pathological cases; most of it is reabsorbed by the intestinal mucosa. Hemmeler[155] calculated that the biliary excretion of iron fluctuates between 5 and 28 mg.; it is independent of the serum iron level and does not acquire any practical importance.

The iron content of the urine is nearly naught. Hemoglobin that could arrive at the renal tubules is destroyed; its iron is not excreted but is transformed in ferritin. The plasma iron cannot trespass the glomerular barrier, being bound to transferrin. An intravenous surcharge of iron yields a negligible urinary iron excretion; if the metal is radioactive, the urine shows at most a very feeble radioactivity. An exception, however, is realized in the nephrotic syndrome. The electrophoresis and subsequent autoradiography of the urinary proteins mixed with iron isotopes demonstrate the presence of appreciable quantities of transferrin. The same anomaly is present in the proteinuria of heart failure. These patients may thus lose an important amount of iron through the urinary tract.[55,253]

In total, taking into account the losses by sweat, cellular desquamation, and hair and nails, the iron elimination does never exceed 1 mg. per day.

Nevertheless, this statement holds true only for men. Adult women suffer with each menstruation a loss varying between 25 and 100 mg. of iron. Their iron balance is still more threatened, as pregnancy and lactation too require an important amount of the metal. These losses are compensated by a highly increased digestive absorption, but an insufficient intake or a difficulty in absorption will suffice to create a deficiency. In opposition to men, women are particularly exposed to sideropenia.

The Normal Sideremia

The serum iron level remains constant, not by excretion of the surplus but by fluctuations of the iron stores. It is absolutely independent of the hemoglobin level.[79,150,165]

The contents of the preceding sections make it clear that the serum iron turnover is intense, i. e., that the iron transit through the blood serum is important. It depends chiefly on the activity of the erythropoietic bone marrow and less on the degree of hemolysis and the extent of the iron stores.[35] A first approximation of it is obtained by the estimation of the serum iron.

Most techniques of serum iron dosage proceed from Heilmeyer and Plötner's original method. I utilize Lederer's modification.[211] Normal values are estimated in very different figures by the diverse authors (Table 1). The limits of normal, as some papers like Vahlquist's estimate them,[358] are surprising. With Benda, I express scepticism concerning such a large scope of variability. This is also Heilmeyer's opinion[147]; he believes that the serum iron level is nearly constant and that its maximum normal deviation is of $\pm 30\%$. The cause of the dispersion of figures called normal depends on several factors inherent in the way of manipulating the blood samples, in the examined persons, in the various countries, in food habits, etc.

Variations of Serum Iron.—1. Table 1 clearly shows a sexual difference. It will be discussed in the section concerning endocrine influences.

TABLE 1.—*Normal Values of Serum Iron According to the Literature*

Authors	Serum Iron, μg. % Men	Women	Notes
Albers [5]	—	91	
Andersson [6]	115	105	Inferior normal value 60–70
Bickel [21]	125	90	
Boulin [26]	126	89	
Brendstrup [29]	125	101	
Brøchner-Mortensen [41]	132	127	
Chaloupka [56]	—	116	
Christian [67]	166	125	Normal between 70 and 286
Dahl [71]	130	110	
Dejardin [79]	111–146	98–130	
Dreyfus [87]	140	110	
Fowler [100]	111	92	
Guischard [121]	126	89	
Heilmeyer [147]	141	118	
Hemmeler [155]	123	109	
Hoet & Lederer [170]	141	118	
Høyer [183]	129	113	
Indovina [198]	100–130	90–120	
Jasinski [173]	100	140	
Kooyman [186, 187]	118–142	88–127	Normal between 25 and 300 (!)
Laurell [207]	124	108	
Locke [226]	100	77	
Rustung [303]	119	102	
Schlaphoff [315]	—	77	
Tötterman [344]	140	121	
Vahlquist [358]	142	123	Normal between 60 and 273

2. Vahlquist [358] first described the fluctuations of serum iron during the day. The lowest value is usually found in the evening, the highest, in the morning. Hemmeler [155] finds the lowest figures at 18 hours, the highest, at 8 hours. A sleepless night or an insufficient bed rest produces a fall of the serum iron value. The inversion of diurnal life rhythm (night-watchmen, for example) is rapidly followed by an inversion of the sideremic oscillations. The rise of the morning concentration could be the consequence of a predominating parasympathetic activity, the vesperal decrease depending on an orthosympathetic control.[155,310] Every neurovegetative imbalance may be accompanied by a corresponding change in ferriemia. Hamilton et al.[139] describe very great nyctohemeral oscillations of serum iron. Their mean value in man at 9 a. m. is 148μg. % and at 9 p. m., 66μg. %. The rhythm of these fluctuations may be inverted without any apparent reason; anyway, it is always independent on the initial level. It may be demonstrated as well during acute hepatitis as in anemias of infection. The same authors believe there exists a relation between that phenomenon and suprarenal activity. The excretion of adrenocortical steroids is indeed most intense in the morning and varies also during the day. They observe, nevertheless, a classical curve of sideremic variations in two patients with Addison's disease; Larsen and Lassen [204] could even demonstrate it in an adrenalectomized woman.

It is curious that the changes of the serum iron concentration take place without a parallel variation of serum transferrin, copper, sodium, or potassium. They are, nevertheless, a part of a general biological rhythm, manifested by the heart frequency, glycemia, gastric secretion,[322] and even heart metabolism.[72] Laurell, observing analogous variations of bilirubinemia, attributes the fluctuations of sideremia to an accelerated destruction of erythrocytes during the night.

3. An intense muscular exertion provokes an elevation of ferriemia, due to effort hemolysis (that may sometimes be responsible of hemoglobinuria).[32]

4. Menstruations do not alter the serum iron. Albers showed a discreet tendency to a decrease, but the variations are devoid of statistical significance.

Surcharge Curves.—1. Administration per Os: These are realized by administrating bivalent iron by mouth and dosing the sideremia at the start and two, four and sometimes six hours later. As shown in Table 2, the maximum elevation goes from 30μg. % to 160μg. %.

One has to remind oneself of the spontaneous nyctohemeral variations while interpreting the curves. Besides, the rapid fixation of iron by tissues may alter the results; this is the case in hemochromatosis.

TABLE 2.—*Elevation in Serum Iron with Administration of Bivalent Iron by Mouth*

	Serum Iron μg. % Initial Value	After 2 Hr.	After 4 Hr.
Lambrechts et al. [192]	118–139	152–184	148–180
Ossipovski [265]	115	240	250
Cartwright & Wintrobe [297]	Mean elevation of 100 μg. % between the 2d & 6th hr.		

In iron-deficiency anemias the curve shows a steep rise; in anemias of infection or tumors, though the initial value is low, there never occurs an important elevation of sideremia.

2. Intravenous Administration: The curves are established by injection of soluble ionized iron and dosage of serum iron after determined intervals. The blood samples should be taken from another vein for fear of contamination with iron. The following results are mentioned:

Laurell.[207] The sideremia passes to 147μg. % to 243μg. % in four hours (mean numbers in 10 subjects).

Ossipovski.[265] Mean elevation was from 380μg. % after five minutes and to 280μg. % after one hour.

Cartwright and Wintrobe.[397] Elevation of the initial figures was between 170μg. % and 230μg. %; the return to normal lasts 8 to 12 hours.

Within certain limits the first surcharge test gives an account of the quality of digestive absorption, the second, of the rapidity of tissular fixation. The interpretation of a tolerance curve is nevertheless difficult! In the first type of experience an absence of variation may indicate that no absorption takes place but also that the iron leaves the blood stream immediately after trespassing the intestinal mucosa.[180] The same subject may manifest at different moments very different curves without any apparent cause.

Iron Metabolism in Pregnancy

Gravidity requires about 400 mg. of iron. It is therefore not surprising that Lund found that more than half of 4000 pregnant women studied suffered from iron-deficiency anemia. Mayer and Dreyfus drew the same conclusions. This anemia may be prevented by systematic administration of at least 15 mg. of iron daily during pregnancy.

The extra needs of gestation are compensated by a considerable increase of the digestive absorption (the activity of which is efficient only if the alimentation is adequate). Studies with iron isotopes demonstrate that the digestive absorption improves more than three times, especially during the second half of pregnancy.[137,207] The requirements are 1 mg. per day during the first trimester, 4 mg. during the second, and from 12 to 15 mg. during the third.[283] The plasma transferrin concentration is considerably elevated.

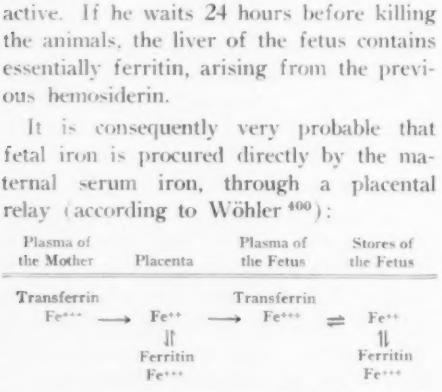
A hematopoietic criterion is difficult to establish during pregnancy. There is hemodilution with pseudoanemia, so that the inferior limits of normal average 3,500,000 erythrocytes per cubic millimeter and 10 gm. % of hemoglobin, i. e., 64% of normal. The normal value of sideremia also is much discussed, for the same reasons. Many authors estimate that the serum iron is diminished in pregnancy.[147,211,257,283] Laurell[207] finds normal figures during the first months and a subsequent fall; he quotes other writers who describe a sometimes severe hyposideremia during the two last months. Others think, on the contrary, that sideremia increases slightly during gestation, particularly in the last months,[264] although a final depletion of the stores may induce a fall.[155] Alberts[2] and Kojima (cited by Vannotti[365]) assert that the serum iron is constantly elevated during childbearing because of the mobilization of the stocks. The German author is so convinced of that elevation that he preconizes it as a sign of pregnancy that becomes positive earlier than the Aschheim-Zondek test. He affirms, furthermore, that, even without abortion, the sideremia returns to normal some minutes after the death of the fetus.

In about eight weeks after delivery the serum iron concentration becomes normal again.[228]

Notwithstanding the evidence that the fetus receives its iron from its mother, the way of transplacental passage kept a mysterious aspect that only begins to fade. An ancient opinion was that the placenta phagocytized maternal erythrocytes and hemolyzed them to put iron at the disposal

of the fetus. In 1942, Pommerenke et al. published that iron isotopes given to the mother at the moment of delivery may be detected sometimes as early as 40 minutes later in the child. A direct transplacental passage was therefore suspected. Wöhler injects intravenous iron isotopes into gravid rabbits; he finds it back 40 minutes later in the maternal placenta as ferritin and in the fetal liver as hemosiderin, both radioactive. If he waits 24 hours before killing the animals, the liver of the fetus contains essentially ferritin, arising from the previous hemosiderin.

It is consequently very probable that fetal iron is procured directly by the maternal serum iron, through a placental relay (according to Wöhler [400]):



The human fetus presents ferritin in the liver and often in the spleen and the placenta already in the third month.[278] A relative lack of maternal iron is not an impediment to the transfer of important amounts of it to the fetus! Vahlquist [358] showed that the sideremia of mother and fetus evolve in opposite ways. In the latter, its value is low during the first five months and then grows steadily, reaching 160μg. % at delivery: this level is, at that moment, twice that of the mother. Albers insists upon the utmost importance of controlling pregnant women's serum iron: every mother's sideropenia will reflect itself infallibly in the child, not at the moment of birth but later. This will even be so if the maternal deficiency is only apparent as in infections (tuberculosis and chiefly urinary inflammations). The practical importance of these facts is too often neglected.

Iron Metabolism in Hepatic Affections

The biggest iron store of the body is in the liver: It contains approximately half of the reserves, i. e., 400 mg. It interferes in two ways with the metabolism of iron:

1. It accepts the circulating iron set free by the disintegration of hemoglobin in the reticuloendothelial tissues. It enables iron to be taken up for renewed hemoglobin synthesis (copper as a catalyst is indispensable to that transformation).

2. It plays a direct role in the hemolytic process.

A. Acute Hepatitis.—Warburg and Krebs first demonstrated an elevation of serum iron in acute hepatitis. This has been confirmed since. The sideremia may reach four times the normal value; ordinarily it exceeds 200μg. %.[15,57,143,151,155,195,225,244,330,358,365] During the first two weeks the rise is gradual but in general insufficient to confirm the diagnosis. In the febrile preicteric phase, Heilmeyer could even show a transitory fall of the sideremia just as in every infectious process. The hypersideremia is most intense at the beginning of the 3d week; it persists from the 4th till to the 8th week, then goes down in a wavering manner until the 12th week. It lasts often longer than the jaundice.

In general, the maximum level coincides with the acme of the disease, usually when bilirubinemia is highest. There is, however, no correlation between serum concentrations of iron and of bilirubin in hepatitis; the first rises more slowly and remains elevated a longer time; serum iron increases even in anicteric hepatitis. Nor is there a relation between the severity of the disease and the iron concentration.

To have any diagnostic significance in this affection, the following conditions are required from the serum iron level: (1) to be sufficiently high, surpassing 200μg. %; (2) to last a relatively long time.

Based on these criteria, the test is accurate (between 80% and 90% of exactness in Atzmon's series).

Notwithstanding this elevation of serum iron, the transferrin concentration rises still more. The braking effect is obtained with difficulty.[85,161] There is a narrow

relation between this phenomenon and the elevation of β-globulins, as transferrin belongs to these proteins.

The pathogenesis of hypersideremia in acute hepatitis appears clearly related to the phase of acute hepatocellular necrosis in the disease. These facts were already established experimentally by Vannotti and Delachaux; they received confirmation by Reismann et al., who induced a toxic hepatitis in dogs by means of carbon tetrachloride and who could demonstrate that (*a*) the rise of the sideremia begins at the same moment as the parenchymatous destruction; (*b*) the correlation between the degree of necrosis and the height of serum iron is outstanding; (*c*) there is no correlation between serum iron and other hepatic tests, such as prothrombin time sulfobromophthalein excretion, and flocculation tests.[225]

In conclusion, the increase of circulating iron has a double origin:

1. It results from the liberation, by cellular disintegration, of the iron normally stored in the liver. Another proof thereof is brought by Heilmeyer[146]; in a case of human intoxication with carbon tetrachloride, serum iron rose to 1750μg. %; hepatic necrosis was so severe that even the liver ferritin got poured out into the blood stream, whence it could be separated.

2. The functional incapacity of the impaired liver parenchyma leaves in the circulation the iron liberated by the physiological hemolysis. An intravenous injection of iron produces a far more important elevation of sideremia than normal, due to the increase of the total iron-binding capacity. Furthermore, that elevation remains much longer. Scholl's and Weinmann's researches produced the following results (in micrograms per cent):

	Before Injection	After Injection, Hr.		
		2	4	8
Normal	140	240	180	140
Acute hepatitis	190	440	340	300

These authors consider these intravenous tolerance curves to be specific for acute hepatitis.

Hemmeler[151] thought the obstruction of the bile ducts to be due to the hypersideremia of acute hepatitis. The absence of increase of the ferriemia during mechanical obstruction of bile ducts in pathological circumstances or experimentally by ligation proves the fallacy of this hypothesis.

According to some,[225] simple hypoxia of the liver tissue could alter the ferritin metabolism and consequently the deposition of iron in the liver.

How can the falsely negative results be explained? They may depend on a severe lack of iron or mostly on the existence of an intercurrent inflammation or a cancer (that both inhibit the increase of the serum iron level). This is the reason why Weil's infectious jaundice passes away without hypersideremia.

In chronic relapsing hepatitis, the serum iron behavior is similar to that in acute hepatitis but with fewer characteristic values.[195]

B. Cirrhosis.—In most publications, the serum iron is said to be normal or slightly diminished. The total iron-binding capacity is in general clearly decreased. The difference from acute hepatitis proceeds from complex factors, comprising disturbances of digestive absorption, dysproteinemia, and general deficiency and also the simultaneous alterations of the hepatic parenchyma and its reticuloendothelial system. A hemorrhagic tendency may sometimes still complicate the metabolism of iron.

The intravenous hypersideremia curve allows the distinction between an ordinary cirrhosis and hemochromatosis. In the latter, serum iron generally is low and the transferrin level, decreased. The saturation coefficient is high; symptoms of iron poisoning occur early during the injection. In cirrhosis, on the contrary, the saturation coefficient is normal or slightly diminished.[115]

If the cirrhosis enters in a necrotic phase, the serum iron rises with a direct proportion to the degree of acute cellular destruction.[57]

C. Biliary Obstruction.—Whatever may be the nature of the obstacle (lithiasis, angiocholitis, benign or malignant neoplastic compression), it depresses the serum iron level. While, indeed, the parenchymatous liver functions are intact, most biliary obstructions cause a more or less manifest local inflammation and therefore a fall of ferriemia; besides, cancers by themselves diminish sideremia.

D. Hepatic Coma and Acute Yellow Atrophy.—These two states are accompanied by a steep fall of serum iron,[155] indicating a very grave prognosis. According to Heilmeyer, this lowering is due to the acute stress of the affection.[143]

It is thus clear that the estimation of serum iron gives precious and precise informations concerning most hepatic disorders, especially because they are related to other liver functions than those usually tested.

Hemochromatosis

It would not be possible to make the point of our knowledge of iron metabolism without mentioning briefly the recent acquisitions concerning hemochromatosis. As is well known, this is a disease characterized by a general accumulation of iron with fibrosis of several parenchymes resulting in disturbances of their functions. The synonyms of *bronzed diabetes* and *pigmentary cirrhosis* have been a bad choice; they concern symptoms that are not an obligatory part of the disease.

The male sex pays the heaviest contribution (sex ratio, 20:1). During the 30 years of their sexual maturity, women lose indeed between 10 and 15 gm. of iron through menstruations. The losses that sentence them to iron-deficiency anemia save them from hemochromatosis, states Kalk.[179] The disease is found only in amenorrheic females and mostly at an advanced age.

Hemochromatosis is different from siderosis encountered, for instance, in hemolytic anemias; it is not a question of displacement of the body iron but an augmentation of the absolute amount of that metal. In both cases, however, there is hemosiderin.

This pigment especially infiltrates the liver (the iron content of which rises to 20 to 50 times that of normal), the pancreas, and the peritoneal lymph nodes, principally those situated near the liver (drainage of intestinal lymph to the liver?). It invades in a variable way the salivary glands, the endocrines (anterior hypophysis, thyroid, parathyroids, adrenal cortex, and gonads), the myocardium, the lungs, the skin, the digestive mucosa, and the bone marrow. On the contrary, it touches but seldom the kidneys and the spleen, even when the latter is considerably charged by hemosiderin in hemolytic accidents.

There is no pathological accumulation of iron in organs that do not normally contain a store of the metal; hemochromatosis leaves intact the striated muscles but not the myocardium, where there always is a minute reserve of iron.

Physiopathology.—It is beyond all doubt that the illness cannot come from an insufficient iron elimination, since the metal is not excreted.

Studies with radioactive iron showed that the digestive absorption is greatly increased.[88] Heilmeyer repeated those experiences with Fe^{55} and Fe^{59} given by mouth.[143-145] A normal man retains at most 10% of the administrated dose; in hemochromatosis, the assimilation reaches 30% and even 50%. Nevertheless, the part of that absorbed iron destined to erythropoiesis is minimal—0.7% or 0.8%. Bothwell[34] arrived at the same conclusions. Thus it is evident that the intestinal barrier opposed to an excessive iron absorption is run over. The liver constitutes a second barrier but is rapidly overcome.

How may such an invasion be explained?

1. It has been thought that the formation of apoferritin was disturbed and so the ef-

ficiency of the mucosal block was limited. Michaels and Granick cited by Remy [289] and Heilmeyer [143] found, however, normal ferritin in the duodenum, liver, and spleen in hemochromatosis patients. Recently, abnormally high ferritin concentrations have been described in the disease.[146]

2. A displacement of the oxidoreduction potential could allow the ferrous ions to transgress rapidly the intestinal mucosa.

3. Taylor et al. (cited by Heilmeyer [144]) announced that the removal of the pancreas or the ligation of its excretory ducts favors iron absorption in the cat. These experiences await confirmation.

4. An ill-balanced diet may sometimes be incriminated. It is known that a lack of protein and phosphorus brings about an overload of iron by increase of the intestinal absorption in the rat. [181]

The alteration of the iron metabolism, however, makes out only one of the characteristics of hemochromatosis. Several other pigments are involved in hemochromatosis and their significance is still not clearly understand. Besides *hemosiderin*, there is [237] (*a*) *hemofuscin*, possibly a lipofuscin, but different from the usual kind (according to Oebicke it could be the precursor of hemosiderin), (*b*) ordinary *lipofuscin*, and (*c*) *melanin*.

Oebicke estimates that the four pigments have a common origin: hemoglobin, that would be destroyed and metabolized differently in such diverse tissues as ectoderm, reticuloendothelial tissue, and smooth musculature. In general, the confusion in the knowledge of those pigments still is "Babylonian." [141] Nevertheless, one may consider that besides the disturbance of the iron metabolism, there is a second alteration involving the metabolism of certain proteins and lipids. Askanazy (cited by Hedinger [141]) therefore could define hemochromatosis as a "polypigmental polysclerosis."

Etiology.—A constitutional and hereditary element constitutes the basis of the disease (bibliography in Kalk [179]), hence Sheldon's etiological summary: "an inborn error of metabolism, congenital in origin." A particularly eloquent genealogical tree is exposed, for example, by Boulin and Bamberger.

Some authors, like Kalk, believe nevertheless in the acquired origin of certain cases of hemochromatosis. It cannot be denied that certain external factors have a deleterious influence. The question is whether these factors reveal a hemochromatosis or are really capable to create it.

1. One of them is chronic alcoholism. It could lead to hemochromatosis through stages of liver steatosis first and cirrhosis afterward.

2. The action of metals, such as copper, arsenic, and lead, could be similar. The patient's anamnesis frequently mentions manipulations of copper. Hemochromatosis seems to be more prevalent in copper-industry workers than in the rest of the population.[179,229,230,231]

3. Hepatitis may have the same effect as both preceding factors.

4. A severe alimentary deficiency (hunger dystrophy). Schwietzer demonstrated that a lack of proteins augments the digestive resorption of iron [325]; besides, every relative shortcoming of proteins and/or every excess of iron finally trespasses the upper limits of possible ferritin formation—hence a precipitation of the iron as hemosiderin, poorer in proteins but richer in iron. Heilmeyer called this phenomenon "siderophanerosis." [146] Hemochromatosis has been frequently encountered in war prisoners. Kalk affirms that severe dietetic privations suffice to produce hemochromatosis. The melting away of tissues, principally of muscles, with subsequent destruction of myoglobin, surely could provoke liver siderosis. In two of such cases, Kalk certifies that repeated liver exploratory punctures demonstrated a progressive sclerosis of the parenchyma. He could produce in rats a disease comparable to hemochromatosis by giving the animals a low-protein diet; Taylor et al. (cited by Masshoff [237]) obtained

the same results. Kalk assumes that every cirrhosis leads to hemochromatosis but that most cases do not follow a complete evolution.

Gillman and Gillman [113] described a liver sclerosis in pellagra of Bantu Negroes; this population eats foods rich in iron (Walker and Arvidsson, cited by Kalk [179]).

Though it is generally accepted that a serious undernutrition of long duration may result in hepatic siderosis, there is no unanimity to admit that such a surcharge ends with real hemochromatosis. Masshoff,[237] for instance, believes that *cytosiderosis* leads to a genuine pigmentary cirrhosis but not to general hemochromatosis; there is indeed neither pancreatic fibrosis nor diabetes mellitus; furthermore, the disease occurs mostly in young males. *Cytosiderin* would be a distinct pigment, allied to hemofuscin and lipofuscin on the one hand and to hemosiderin on the other hand.

Multiple transfusions also create hemosiderosis without hemochromatosis.[179,237] They may, however, make evident a latent hemochromatosis. Animal experiences lead to the same conclusions (Cottier, cited by Masshoff [237]).

These cases of cytosiderosis, however, state several problems.

1. The total amount of liver iron often exceeds the quantity of injected iron in transfusion siderosis. This occurs in aplastic anemias, where the hypoxia provokes an increase of iron resorption. Peroral administration of iron is therefore of questionable value in such anemias. It is certain that in general every treatment with intravenous iron ought to be short.

2. In a case of hemosiderosis related by Heilmeyer,[145] the radioactive iron was absorbed by the intestine as greedily as in true hemochromatosis. Bothwell et al.[34] however, publish results demonstrating that the digestive absorption of iron slackens in dystrophic cytosiderosis and transfusion hemosiderosis.

We may thus infer that if hemochromatosis generally is a congenital disease its acquired origin may be conjectured but not affirmed. At any rate, hemochromatosis is a dystrophia by accumulation; this *thesaurismosis* [145] affects not only iron but also pigments and even copper (the concentration of which is indeed always elevated in the blood).

There is no unanimity about the source of the sclerosis. Some say it is secondary to the cellular degeneration induced by pigmentary overload; others believe that siderosis and fibrosis are two independant processes.

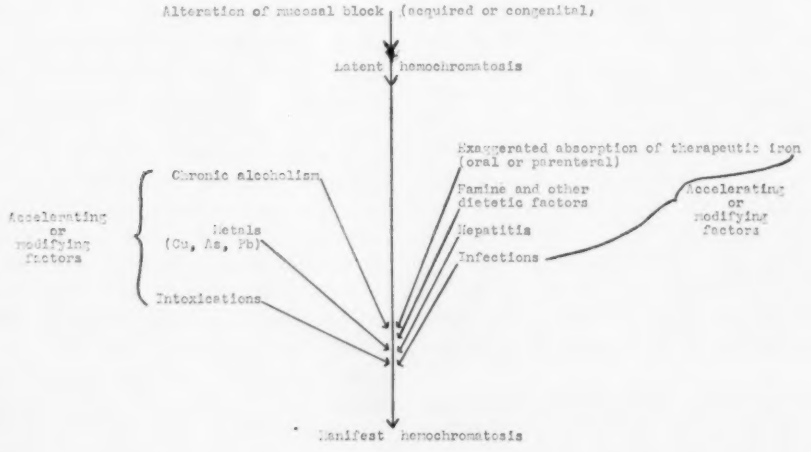


Figure 1

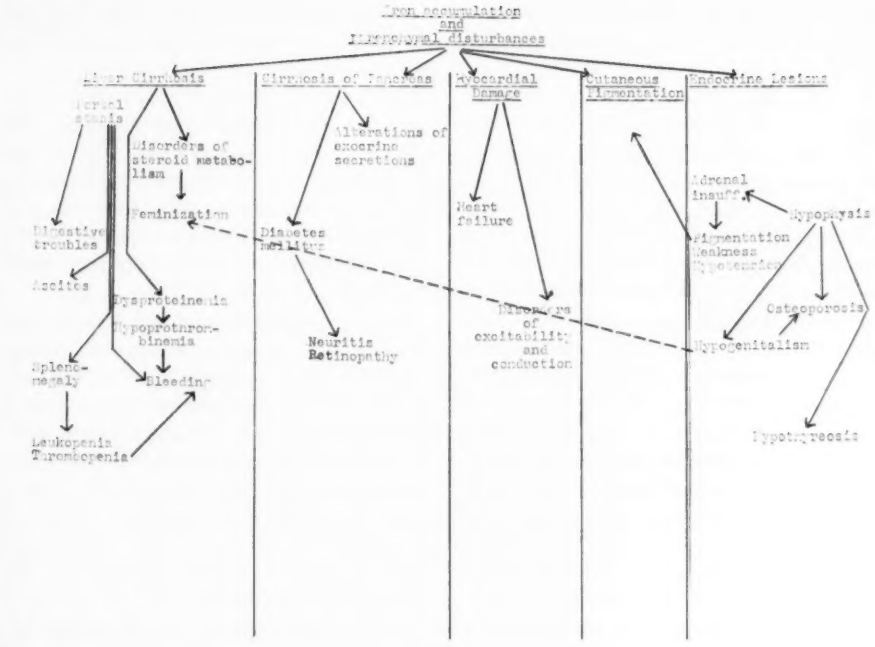


Figure 2

Figure 1 (according to Heilmeyer [143,144]) sums up the etiological factors in hemochromatosis.

The *symptomatology* is sketched in Figure 2 (according to Heilmeyer [143,144]) but deserves commentary.

1. *Liver cirrhosis* is not a constant feature. Kalk describes four cases of verified hemochromatosis where the liver presented a simple siderosis without sclerosis; only repeated exploratory punctures revealed the gradual establishment of fibrosis. At first, iron accumulates in the peripheral cells of the hepatic lobule; it invades the center progressively and infiltrates the Kupffer cells, while sclerosis supervenes. Pirart and Carpent also describe a genuine liver siderosis without sclerosis in initial hemochromatosis.[273]

The liver tests become positive only after definitive establishment of the cirrhosis.

2. The *pigmentation*, too, is variable. While Sheldon did not find it in 25% of his cases, Heilmeyer misses it only in 4%. It occurs principally in the cutaneous areas exposed to light but never touches the mucosae. Its color may have a double origin—it is composed on the one hand of a melanin tattooing of the inferior epidermic cells and on the other hand of an inconstant hemosiderin infiltration into the hypodermis.

3. One case out of five displays no *diabetes*. This is always a late symptom that remains latent in an additional 15% of people; it is thus frankly present in two-thirds of the patients only.[144] It is not yet known how far the antehypophysis and the adrenals partake of the disturbance of carbohydrate metabolism. The diabetes may indeed be light and benign, without acidosis, or, on the contrary, serious because of resisting hundreds of insulin units. Anyway, the apparition of diabetes is a grave complication; it reduces the life expectancy to 18½ months in Sheldon's experience, and to 4 years in Boulin's.

4. The lesions of the *exocrine pancreas* produce creatorrhea and steatorrhea; they are very rare.

5. The *endocrine disturbances* are as follows.

Hypogenitalism is present in one out of two cases. As in an ordinary liver cirrhosis, it is attributed to insufficient hepatic inactivation of the female hormones secreted by the adrenals. Hemochromatosis of the testicles is unusual; the male gonad atrophy is secondary to pituitary insufficiency. This may be demonstrated by the considerable decrease of the level of hypophyseal gonadotropins.[220,288]

Testosterone injections may sometimes induce a considerable amelioration in hemochromatosis patients; at the same time there is a fall of the sideremia and injected iron disappears faster from the serum. These effects are transitory, due to an augmentation of the muscles and myoglobin synthesis. The result of this treatment is inherent to the general anabolizing power of the male hormone.[220]

The adrenals may degenerate without being touched directly by the disease. This is one of the possible causes of cutaneous pigmentation. Suprarenal insufficiency, like hypothyreosis, proceeds from disturbances of pituitary function.

6. There are also *hematological alterations.* The hemoglobin concentration and erythrocyte and reticulocyte numbers are normal or slightly diminished. A posthemorrhagic anemia (due to esophagal varices, for instance) heals swiftly. Splenomegaly is often complicated by hypersplenism; while the iron supersaturation assures an immediate compensatory erythropoiesis, leukopenia and thrombopenia are rather frequent.

7. The possible absence of *hypersideremia* should be stressed, although the elevation of the serum iron level is one of the most characteristic symptoms. It may indeed be masked by a simultaneous infection or malignant neoplasm. We remember in particular one case where hemochromatosis has been questioned on account of a ferriemia constantly lower than normal; besides hemochromatosis, necropsy demonstrated an extended bile duct cancer. Heilmeyer expresses the same conclusion[143]; he mentions the absence of hypersideremia in three patients whose illness was complicated by infection. Failure to appreciate this possibility is responsible for publication of very diverse serum iron levels in hemochromatosis (see, for instance, Christian[57]).

Serum transferrin is always diminished; its saturation coefficient approaches 100%. The oral iron surcharge curve therefore remains flat, notwithstanding an exaggerated digestive absorption. This explains why formerly the iron absorption was said to be diminished in hemochromatosis—the metal leaves the plasma very rapidly. After an intravenous injection, its concentration returns to normal in six hours, i. e., as quickly as in infections.

8. As in several other hepatic affections, hemochromatosis may produce an abnormal porphyrinuria (especially of coproporphyrin Type I). This explains perhaps the distribution of cutaneous pigmentation. There may also exist a photodermatosis.[342]

9. Cardiac disturbances are so frequent that 8 or 9 out of 10 patients suffer them.[144] They are caused by the deposit of hemosiderin and myocardic fibrosis. They present themselves as disturbances of the excitability and of the conduction. They may result in heart decompensation.

The *treatment* of hemochromatosis made progress as a result of Davis' and Arrowsmith's investigations based on the pathogeny of the disease. They propose to withdraw the excess of iron by repeated venesections of 500 cu. cm.; every other day the separated plasma is reinfused. They arrive thus at a fall of hemoglobin to 10 or 11 gm. % and of erythrocytes to 3 or 3.5×10^6 per cubic millimeter. At this moment the bleedings are separated by intervals of four to eight days. In that way, each patient loses between 25 and 45 liters of blood in a year; he absorbs a diet compris-

ing daily 500 gm. of carbohydrates, 150 gm. of lipids, and 200 gm. of proteins. This treatment has since been applied universally, sometimes with surprising results. The patient's general status may improve so much that he resumes his work. The hepatomegaly regresses, as does cutaneous pigmentation. Liver exploratory punctures show the regression of hemosiderin infiltration, the sclerosis being irreversible.

A reserve statement should be made. A hemosiderin deposit of long duration suffers an aging process; the micelles tend to precipitate and convert themselves to *goethite*, an inorganic insoluble iron compound.[326] Experience shows that at this time the metal cannot be demonstrated.

More recently edathamil has been proposed in the therapy of the diseases due to an iron overload. Given as its disodium salt, it combines with iron into nonionized complexes that are excreted by the kidneys. Until now its use has been discouraging; in therapeutic doses the iron elimination (about 3.75 mg. daily) is too poor to influence the course of the disease.[399] Besides, the administration of the substance provokes an important fall of prothrombin time, notwithstanding its association with vitamin K. Its practical application is therefore not actually realizable.

Relationships Between Endocrine Secretions, Iron Metabolism, and Erythropoiesis

Anemias of endocrine origin are relatively rare. The disturbance of internal secretions does not necessarily have erythopoietic repercussions; the appreciation of both phenomena is besides very difficult, as pathological endocrine manifestations may be the consequence of the anemia. It is probable, for instance, that the ovarian alterations in sideropenic hypochromic anemia are not the cause but the consequence of that deficiency.[313]

An intervention of internal secretory glands upon erythropoiesis and iron metabolism has been generally recognized since Naegeli. Pluriglandular affections especially produce alterations of the blood. An anomaly of one single secretion appears to be well tolerated from that point of view.[147,175] Sharp and Mack confirmed this fact several years ago: in 110 women where anemia and endocrine disorders were associated they found a combination of hypothyroidism, pituitary insufficiency, and hypogonadism; in every case the anemia supervened after exaggerated genital blood losses.

A systematic study of iron metabolism in endocrine disorders has not yet been undertaken and for very good reasons. The same observer has indeed not the opportunity to investigate a sufficient number of human cases that allow him to draw pertinent conclusions. On the other hand, the experiences in the laboratory often give contradictory results because of the complexity of the problems; besides, one perceives that too often the results may not be applied to man.

1. *The Ovary.*—The results of the experiences related by diverse authors are astonishingly discordant. One may indeed read that the injection of estrogens in the *rat* diminishes the reticulocytosis without altering the number of erythrocytes [8]; produces an anemia by hypoplasia of the bone marrow [11,337,369] with histological pictures of marrow hypoplasia; is responsible for transitory anemia, repaired after a reticulocytic crisis two weeks later, the marrow being adapted [37]; and provokes an anemia only when associated with progesterone.[188] Other observers, on the contrary, give evidence of estrogen stimulation of blood building! [97,201] A fall of serum iron has been described after the administration of estrone or estradiol.[171]

In the *ape*, these female hormones do not have the least effect.[62,357] In *dogs* the use of folliculin is followed regularly by a progressive normochromic anemia from the second week on. The animals die finally with thrombopenic purpura. It has been showed that this is due to idiosyncrasy; the results may not be compared to those ob-

tained in other animal species.[9,20,65,201,318] In *guinea pigs* there is no statistically significant hematological modification after estrogen administration,[201] or in *rabbits* either, although the number of reticulocytes may diminish.[260]

Castration of female animals, too, has such discordant consequences that they may not be taken in consideration.[11] They depend surely on multiple conditions, such as the age of the animals and their alimentation. While in America Daughaday et al.[75] and Steinglass et al.[337] observed after the operation a rise of the erythrocyte count that may be reduced again by injections of diethylstilbestrol, von Falkenhausen,[92] in Germany, obtained a fall of erythrocytes and hemoglobin. It seems certain that after oophorectomy a posthemorrhagic anemia requires thrice the time to heal if compared with that in normal animals.[92,147]

Schwarzhoff, after ligation experiences on the ovarian pedicle, concludes that the estrogens are practically devoid of erythropoiectic effects but that the ovaries produce a substance, absolutely distinct from sexual hormones, that may stimulate the bone marrow production. Its secretion should be under the control of hypophyseal prolan.[323,324]

In the human being, the number of erythrocytes and the hemoglobin and serum iron levels are constantly lower in women than in men. Male tissues are richer in iron than female. For the following reasons the male sexual hormone seems to be responsible for that difference:

1. Before puberty, sideremia and erythrocyte values are identical in both sexes; this is true also beyond 60 years but not immediately after the menopause. This fact excludes the probability of possible intervention of menstruations!

2. The serum iron level does not change in females either before or after the menarche or even after the climacteric. In males it rises with the onset of sexual endocrine activity.[11,155,359] Albers describes at puberty an augmentation of serum iron in both sexes, but it is much more observable in boys.

The sexual difference of these values is found in nearly all animals, even those that, like birds, do not menstruate. It is consequently to be considered as a real secondary sex character.

In women, no change has ever been reported after bilateral oophorectomy from a hematological value or in iron metabolism.[171,359] Studying the question recently, Lederer et al.[219,220] demonstrated that the observed differences are too small to be significant. A counterproof treatment did not bring any result either.

To conclude, I can only state that the results of the sexual endocrine influence are disparate as well in the laboratory as in human medicine. The danger of drawing analogies or of extrapolating from one species to another should be emphasized. From the whole of published works, it stands out that high doses of estrogens are a poison for the bone marrow; they are never applied in therapy. In the estimation of the role played naturally by the female sex hormones, two opinions stand face to face: One affirms their depressive property on hematopoiesis (directly or through inhibition of hypophysis), and the other one attributes to them an eutrophic action similar to that of androgens but much less powerful. Their influence on erythropoiesis and on iron metabolism seems practically negligible.

2. *The Testicles.*—Androgens increase the number of red corpuscules, the hematocrit coefficient, and the hemoglobin index of normal senile rats and of adult castrated rats, both male and female.[188,337] Orchiectomy produces a moderate hypochromic anemia, but very inconstantly,[11] and its results are discussed.[64,92,249,380] Testosterone propionate considerably restores the reticulocytosis of hypophysectomized rats, diminishes their anemia, and greatly reduces the bone marrow hypoplasia.

Palmer (cited in an editorial [171]) does not observe any appreciable change of serum iron after testosterone injections in the rat.

As shown before, it seems clear that the androgens are the responsible agents for the sexual differences in erythrocyte and serum iron values.

In humans, Silvestroni and Bianco showed the stimulation of hematopoietic tissues by testosterone in patients of both sexes with hypochromic anemia secondary to blood loss or neoplasm. In confirmation of Palmer's experiments with rats, the human serum iron level does not change with supplementary testosterone. On the other hand, polyglobulism has been described in apparent linkage with virilizing tumors of the ovary.

Some have observed a moderate anemia, hypochromic and microcytic, in eunuchoids.[11] Lederer et al.[219,220] studied seven eunuchs and found in each a low sideremia. They could raise it by corresponding hormonal treatment; at the same time the intestinal resorption increased.

The place occupied by the hypophysis in those complex anemias is difficult to evaluate. Hypochromic microcytic anemia is one of the symptoms of the adiposogenital syndrome; it occurs principally in panhypopituitarism.[11,119,226,239]

In summary, the favorable influence of androgens on erythropoiesis and iron metabolism cannot be denied. It seems to be part of the general anabolizing power of these hormones.

3. *The Hypophysis.*—After hypophysectomy, one finds the following alterations in the experiment animal[10,11,14,28,62,68,110,164,371]: (*a*) a rapid decrease of the number of circulating erythrocytes; (*b*) a microcytic anemia, hypo- or normochromic; (*c*) a fall in the reticulocyte count; (*d*) leukopenia; (*e*) hypoplasia of the bone marrow, touching leukopoiesis but chiefly erythropoiesis; (*f*) hyposideremia, a tendency to tissular siderosis and a slackened digestive iron absorption, confirmed by investigations with iron isotopes.[99]

All these alterations proceed from the removal of the antehypophysis; removal of the neural or the intermediary parts has no influence on the hematological system.

It should be stressed that Heilmeyer[147] succeeded in avoiding all these disturbances in the dog, provided the nervous centers were respected during hypophysectomy. Ruitinga et al.[302] also report that in such conditions the operation is not followed by anemia in their laboratory.

In most human pituitary disorders that bring forth hematological alterations (polyglobulism of adenomas, anemia of Simmond's cachexia), there are signs of simultaneous disturbances of the hypothalamus (alterations of the metabolism of water, carbohydrates and lipids). Hume and Wittenstein also insist on the intimate and almost inseparable relations that unite hypothalamus and hypophysis. The close interrelations between these two centers have been confirmed in the experiments of Bonvallet et al.[33]; a bilateral lesion of the dog's hypothalamus may reproduce a blood picture identical to that in hypophysectomy.

The anemia of hypophysectomy may yield to nonspecific medications, according to publications of former years[63,64,66,75,109,369,370,380]; to iron, especially if associated with copper; to cobalt; to thyroxin and thyroid powder, and to testosterone (but there remains a degree of hypochromia). Only the combination of thyroxin, testosterone, iron, and a hyperprotein diet should be able to repair the anemia completely.

More recent investigations on the contrary display a more specific role of the hypophysis in erythropoiesis. Already in 1906, Carnot and Deflandre made conspicuous, in the blood of a rabbit anemiated by bleeding, a stimulating principle for erythropoiesis; its power was considerable: A few cubic centimeters of the plasma of the bled animal sufficed to create a frank augmentation of the red corpuscule count in another rabbit. This property received a recent confirmation by Erslev. In vitro, the bone marrow is, on the contrary, depressed by hypoxia.[262] The existence of this humoral erythropoietic substance was definitely

established by parabiosis experiments.[22] It has even been isolated from the blood plasma [117,300]; it is distinct from most serum proteins and seems to be thermoresistant.

Evans requires from the organ that produces this principle the following conditions to prove it is indeed the site of that elaboration:

1. The removal of that organ should produce anemia.

2. The same operation should reduce the stimulation of erythropoiesis by hypoxia.

3. The excitation of that organ and the administration of some of its extracts should provoke a real polycythemia.

Only the hypophysis fulfills that criterion. It has been known long since, indeed, that animals deprived of their pituitary do not react any more with the usual polyglobulism to lowered barometric pressures.[68,340] Flaks, Himmel, and Zlotnik published the statement 20 years ago that they had discovered a hematopoietic pituitary hormone that produced polyglobulism in normal and hypophysectomized animals; besides, it was devoid of any other property, as the animals died of cachexia during the experiment.

For many years this theory has been questioned, but recent investigations decided in its favor. In 1938, Querido and Overbeek [268,269] already believed that the combined removals of gonads, spleen, thyroid, and adrenals never could induce a blood picture identical to hypophysectomy. Garcia [109] could set up the following conclusions to his investigations: "The anemia of hypophysectomized animals can be repaired by pituitary feeding . . . and apparently this effect is not mediated through any of the other endocrine glands." The same author [110] could annihilate the anemia of hypophysectomy by daily injections of little doses of corticotropin (ACTH); even normal animals become polycythemic with such a medication.

Contopoulos et al.[59] succeeded then in creating a polyglobulism by oral administration of anterior sheep pituitary to hypophysectomized rats; in the meanwhile there does not occur any symptom of stimulation of the organs influenced by the known pituitary hormones, except in adrenals, the activity of which is undeniably excited. Further experiments showed, however, that the hematopoietic effect of the treatment is not suppressed by bilateral adrenalectomy. The existence of the erythropoietic principle is thus corroborated; it appears that it is linked to corticotropin, though its power is not mediated through an adrenal relay. It may be separated from corticotropin by normal digestion in the gastrointestinal tract, whence it is easily absorbed by the mucosa. Its entity, distinct from corticotropin, is still confirmed by the polyglobulism of adrenalectomized animals at altitudes of 22,000 ft. Besides, at normal altitudes these animals have an important elevation of circulating corticotropin without increase of the red cell number.[361]

It was Justin-Besancon [175,176] who could explain those results. Having in treatment patients whose anemia was caused by pituitary insufficiency, he was unable to obtain any blood improvement with use of iron, cyanocobalamin (vitamin B_{12}) or liver therapy, hyperprotein diet, thyroxin, testosterone, or cortisone. The utilization of corticotropin in protracted intravenous perfusions, on the contrary, was successful. Interpreting this effect by the light of Evans' experiments, he arrived at the conclusion that the pituitary erythropoietic factor, though absolutely specific, accompanies corticotropin. This linkage is respected by most extraction methods for corticotropin but not by all. The erythropoiesis is indeed stimulated by certain commercial preparations of corticotropin but not by all of them; this variation may probably explain why Aschkenasy [11] and Nordenson [261] did not obtain favorable responses to corticotropin administration in pituitary deficiency anemias and why Indovina's [170] results were inconstant.

In summary, former writers concluded that the hypophyseal intervention in hematopoiesis had no specific character and that the absence of the gland acted through the

involution of the peripheral endocrines and the slackening of iron metabolism.[10,11,63,64,66,371] It is now certain that among the pituitary secretions there is one that concerns directly and exclusively the erythropoietic system; it may depend primarily on the central neurovegetative system.

Though the hypophyseal origin of this *hematopoietin* or *erythropoietin* is admitted, it should be stated that the pituitary gland is not the only site of its production. Some control, indeed, persists on erythropoiesis after hypophysectomy[361] and allows a positive response to cobalt and more or less to hypoxia. The blood of hypophysectomized rats does contain erythropoietin, especially after bleeding.[69] Gley has been able to show that erythropoietin may be produced by the spleen of the rat and the thymus of guinea pigs. He extracted it from the liposoluble fraction of the plasma; it is a steroid containing one alcohol and three ketone radicals. Similar substances, like 11-dehydrocortisone and 21-deoxycortisone produce an analogous reticulocytic crisis.[118]

4. *The Suprarenal Glands.*—Experimental adrenalectomy provokes anemia if the animal is kept alive with adequate doses of sodium chloride.[11,62,75,272] If aggravated by blood loss, the anemia heals slowly and incompletely. Its characteristics are hypochromia, marrow hypoplasia, and a considerable hyposideremia.[11,13,140] Simple adrenal demedullation or medullar denervation cannot produce it.

Sundstrom and Michaels describe an elevation of suprarenal weight in the anoxic polycythemia of rats.

In man, the adrenal disorders may trouble the erythropoiesis, though inconstantly. Some examples are polyglobulism of Cushing's syndrome and anemia of Addison's disease.

Epinephrine is devoid of any hematopoietic power. It may, however, excite the adrenal cortex through a hypophyseal stimulation; it produces thus an elevation of the serum iron level, according to Schäfer.[309] This effect is not suppressed by such sympathicolytics as Dibenamine or Hydergine and cannot be explained by a vasomotor mechanism; it could occur through reticuloendothelial activity.

Total suprarenal extracts favor erythropoiesis after adrenalectomy and normalize the serum iron levels. They also reduce the degree of anemia in tumor-bearing rats.[25] In intact animals, on the contrary, they produce a fall of sideremia.[140]

Deoxycorticosterone has no influence on the red blood corpuscules of experimental animals and of men,[11,23] but it is responsible for a significant lowering of serum iron.[140]

Cortisone seems to be efficient against the anemia and hyposideremia following adrenalectomy.[11,110,140] Injected in great quantities, however, in normal animals, cortisone (and certain preparations of corticotropin, too) diminish the serum iron level suddenly.[11,53,140,396] When administered in little doses and continuously, both these hormones stimulate erythropoiesis.[75,86] The problem is in fact very complicated; according to Prinzie's experiments on rabbits, the effect of corticosteroids changes with the kind of sex hormone impregnation of the animal.[281] No correlation exists between the fall in serum iron and the utilized quantity of cortisone or corticotropin. The investigations of Schäfer and of Wintrobe's group have shown that these hormones act through the reticuloendothelial system.

In human medicine, they better the anemia of rheumatoid polyarthritis, acute leukosis, sometimes even with an initial reticulocytic crisis. At the same time, the digestive absorption curves show an important ascent, while the serum transferrin increases. The same phenomena occur during the treatment of collagen diseases.[38] In normal men, cortisone provokes variations of sideremia. According to Bateman, they could depend on the individual endocrine status ("basic endocrine pattern"); this opinion is similar to that of Prinzie.

In human diseases where the sideremia is elevated (acute hepatitis, for example), or unchanged, cortisone and corticotropin usually lower the serum iron level.

The role of the adrenals in erythropoiesis and iron metabolism seems to be a very complicated one. Their intervention has two tendencies:

1. These glands maintain an equilibrium in erythropoiesis and iron metabolism, dependent on the quantity of present corticoid hormone and on the response capacity of the body at the same moment.

2. In acute affections (infections, stress) and in tumors, they slacken both erythropoiesis and iron metabolism.

Cartwright et al.[53] suspect a relation between stress hyposideremia and an excessive adrenal stimulation. They show the rapid disappearance of iron from the serum under the influence of 11-oxysteroids and corticotropin; on the contrary, it remains there longer than normal after adrenalectomy. They suppose that these hormones excite the reticuloendothelial tissue, which then captures the circulating iron. That hypothesis will be discussed while the anemia of infections is studied.

5. *The Thyroid.*—Experimental thyroidectomy reduces the life span of the red corpuscules and alters the functions of the bone marrow. Anemia is inconstant; if present, it is hypoplastic and may be normochromic,[62,350] rarely macrocytic,[75] or even hyperchromic.[189] It is most frequent after certain complications, such as phenylhydrazine intoxication, bleeding, or dietary deficiencies, chiefly in proteins. It may be cured by thyroxin but might also be corrected by cobalt and testosterone; it does not appear as an entirely specific entity.

Thyroidectomy is responsible for a diminution of the uptake of Fe^{59} by erythroid cells and by the bone marrow and also for an elevation of the iron content of liver and especially of the spleen.[16]

Spontaneous human myxedema is accompanied in more than 50% of cases by anemia, achlorhydria, and a slackening of iron resorption.[365] There are three forms of anemia:

(*a*) Hypochromic anemia, often associated with achylia and typical signs of tissular sideropenia (see below). It may be cured by a combination of thyroid treatment and iron.

(*b*) Nonpernicious hyperchromic anemia—the most frequent blood disorder in myxedema. It is never severe; the volume index is slightly over 1. Reticulocytosis and bilirubinemia are normal; the bone marrow does not contain megaloblasts. This type of anemia resists antipernicious treatment but responds specifically to thyroid medication.

(*c*) There is finally a genuine pernicious form; it is exceedingly rare. It differs from Biermer's disease by an unexpectedly low basal metabolism. Hepatotherapy is inefficient as long as thyroxin is not associated.[11,147]

Whatever may be the type of the anemia, there is marrow hypoplasia that responds favorably to male hormones.[75,384]

In congenital athyreosis or after thyroidectomy, anemia supervenes inconstantly in man. As in animals, supplementary pathological circumstances are required: insufficient alimentation, bleeding, and intoxications.

In hypo- or athyreosis, the serum iron level is normal[76,87,155,194] or slightly elevated, for the slowing of the general metabolism brings forth a diminished utilization of iron.[11,221]

Thyrostatics such as thiourea and its derivatives also inhibit the bone marrow.

In the dog, the rabbit, and the guinea pig, thyroid extracts and thyroxin provoke a rise of the number of erythrocytes, with congestion and hyperplasia of the bone marrow; the level of hemoglobin may rise somewhat.[11,189,350] The serum iron diminishes.[267] In thyroidectomized animals, the results are similar but more evident. After hypophysectomy the same treatment activates the bone marrow and produces a

reticulocytosis followed by a tendency to recovery concerning the anemia.

Mansfeld and Sos affirm that they isolated a deproteinized thyroid extract that should be a specific erythropoietic hormone. It is nevertheless true that pure thyroxin has every property of this glandular extract; besides, Baldini and Mauri tried but could not reproduce the erythropoietic results of the former authors.

In man, hyperthyroidism is devoid of important hematological repercussions. Some writers mention an elevation of the total erythrocyte number, with reticulocytosis and marrow hyperactivity (leukopoietic as well as erythropoietic); the physiological hemolysis is perhaps accelerated.

In regard to serum iron values in hyperthyroidism, the opinions are contradictory. Some describe a normal sideremia,[76,155] and others, an elevation of it.[87,194] We fall in with the opinion of Aschkenazy[11] and of Forrattini: serum iron is usually diminished in hyperthyreosis because the metal partakes intensely of the accelerated general metabolism and thus leaves the circulation quickly; hyperthyroidism should furthermore be capable of inhibiting the digestive iron absorption. Lederer[216] also finds a lowered sideremia in thyroid hyperfunction. He relates three cases where the iron deficiency was so intense that it hindered the tissular enzymatic activity and blocked the organic response to thyroid therapy. The hyperthyroidism only became frankly evident as the iron deficiency was cured. A similar case is published by Vannotti and Delachaux.

In conclusion, it is beyond doubt that the thyroid gland and thyroxin stimulate erythropoiesis as well as the metabolism of all other systems. Thyroid activity lowers the sideremia because of an increased demand for iron, not only for erythropoiesis but also to build all the tissular ferments required by the elevation of the metabolism.

The Central Regulation of Erythropoiesis and Iron Metabolism

A needle prick into the striatum, the thalamus, and the hypothalamus provokes immediately a neutrophil leukocytosis and a discharge of immature red blood corpuscles.[11] Lasting lesions of the hypothalamus produce contradictory changes, due to the localization and the extent of the destruction; sometimes there is anemia and sometimes, polyglobulism with hyperhemoglobinemia. The consequences of these injuries may be more than hematological; Bonvallet et al. tried and produced diabetes insipidus in dogs, through bilateral lesions of the hypothalamus; at the same time they found a normochromic anemia, increased fibrinogen level, accelerated sedimentation rate, and fall of the number of erythroblasts. These disorders could not be cured with anterior or posterior hypophyseal extracts.

Human cases are known of polyglobulism accompanying certain diseases of the central nervous system that attack the cerebral base, especially the hypothalamic nuclei. They have been described in tumors or encephalitis.[319] Inversely, severe anemias may be associated with disorders of the central gray nuclei and of the hypothalamus. Aschkenasy[11] relates four cases of optic chiasma arachnoiditis and three cases of juxtapituitary tumors, all of them showing an inhibition of erythropoiesis. Cranial traumas, lumbar or suboccipital punctures, encephalographies, and ventriculographies, often increase suddenly the number of leukocytes and reticulocytes and, afterward, the erythrocyte number and the hemoglobin level.[114,160] The same irritations of the central nervous system produce regularly a fall in sideremia and also variations of the glycemia and the body temperature.[154,155,310] Mies and Richarz describe a variation of the serum iron after excitation of the vestibular system.

We have already shown the possible relations between central neurovegetative ac-

tivity and the diurnal variations of the sideremia.[155,310]

The diencephalon and especially the hypothalamus apparently intervene either through the hypophysis or through neurocrinia. Their action could be imitated by injections of corticotropin. It is demonstrated that in stress this hormone is secreted consequently to diencephalic stimulation. This power of the nervous centers is, however, not limited to eventual corticotropin production. Beer saw, indeed, an absence of leukocytosis after injections of pyrogenic substances if the cervical medulla was cut [22]; the leukocytosis was diminished but not abolished after bilateral splanchnic nerve interruption. The removal of both adrenals does not alter the normal response [23]; a suprarenal intervention only gives a partial explanation for these phenomena.

The existence of a central regulation mechanism of hematopoiesis and of iron metabolism does not leave any doubt. It is probably situated in the hypothalamus, whence diverse ways carry its influences: vegetative impulses along neurological pathways,[301,310] endocrine stimulation, and perhaps neurocrinia. That center is likely at rest in normal conditions and becomes active only in emergencies,[301] where its effects are realized within some hours.

Iron Deficiency

The lack in iron, or "asiderosis," [211,212] is a frequent but too often ignored affection: Waldenström pointed out that 20% of all Scandinavian women suffer from it.

Its signs are as follows:

1. *Hypochromic Anemia.*—The volume index is under 0.9. There is a profound disturbance of the hemoglobin synthesis. The quantity of stercoraceous urobilin is superior to that corresponding to the present hemoglobin concentration. Cartwright [50] established that the formation of the red blood pigment is stopped at the protoporphyrin stage. This porphyrin is indeed present in high amounts in the red cells and returns to normal with iron therapy.

The alterations of hemoglobin synthesis are not alone. The red cell volume is always diminished, although the cellular diameter may be variable. There is microcytosis, normocytosis, or sometimes even slight macrocytosis. The globular thickness is, however, always reduced. Finally, the anomaly conducts to anisocytosis and poikilocytosis.

In the bone marrow, the erythroblasts have greater sizes than normal. While the usual myelogram contains a predominance of orthochromatic normoblasts, here basophilic erythroblasts and proerythroblasts are the most numerous. The maturation process is thus disturbed; besides, the number of reticulocytes regresses and their forms are abnormal (normoblasts).

On close examination, the hematological trouble depending on the sideropenia clearly exceeds the sole alteration of the erythroid cells. In serious cases there is also a leukopenia bearing chiefly on the polynuclear cells. The white cell count may be reduced to 3000 per cubic millimeter.

The existence of the anemia has some particular consequences. One of them concerns the mechanism of cardiovascular compensation. The tissular oxygenation tends to be maintained by an increase of the cardiac output and a peripheral vasodilatation [384]; the anemia may be hidden so that, for instance, a "florid chlorosis" has been described. The heart may be enlarged; some edema frequently accompanies the hypochromic anemias; the confusion with heart failure sometimes exists.

Renal function may degenerate too; urea clearance diminishes; there is a renal vasoconstriction, perhaps as a palliative measure.

2. *Trophic Disorders.*—The nails are fragile, crackle, and grow irregularly. In serious deficiencies they get concave (koilonychia). The skin is rough. It shows fissures and rhagades, chiefly on the angles of the mouth and on the fingers. Eckerström's

paper is of a great interest from this point of view. He described in rather numerous cases of varicose ulcers, uncomplicated by hemorrhages, a sometimes considerably lowered serum iron level; the correction of this deficiency allowed a quicker regression of the cutaneous disorder.

The hair, too, degenerates; it becomes prematurely gray and fine; it breaks and falls out.

3. *Mucous Membranes.*—These are not spared by the epithelial disturbances.

On the tongue, the disease provokes *Hunter's glossitis:* The organ is red, sleek, and devoid of papillas. It resembles closely the glossitis of pernicious anemia and is intensely painful, creating a burning sensation.

The esophagus degenerates like the skin and the tongue; the epithelium crackles and forms very painful rhagades, causing spasm and becoming serious obstacles to deglutition.

The association of the glossitis and the esophagitis with the hypochromic anemia forms the *Plummer-Vinson syndrome.* Waldenström focused attention on the x-ray films of the esophagus in this disease; the profile often shows a fold of the anterior wall, pointing to the center of the viscus at the height of the cricoid cartilage. The pain is localized at this level. The image translates a reflex spasm at the place of the fissures.[373]

The Plummer-Vinson syndrome is considered by many as a precancerous state; this is a supplementary reason to treat it vigorously.[192]

4. *Gastric Achylia.*—Anacidity is present in most sideropenic patients; in half of them it resists histamine. Very often it disappears during the iron therapy; it is one of the causes as well as the consequence of the deficiency. Apperly and Cary[6] believed it could be a consequence of the anemia itself; the recent researches of Apperly[5] showed, nevertheless, that neither the erythrocyte number nor the percentage of hemoglobin have any influence on the ionic concentration of man's gastric juice. It is much more probable that this trouble, too, results from the sideropenia.

5. *Gynecological Disorders.*—Most frequent is uterine bleeding; sometimes there is amenorrhea. They both proceed solely from the iron privation.[147,150,218] Schiassi defends, with a solid argument the hypothesis that the ovary itself is touched by the deficiency and that the uterine disorders follow the ovarian alteration. This opinion has been confirmed by Lederer and Ferrin[218]; the endometrium biopsies of sideropenic women did not reveal any intrinsic pathological aspect.

6. *Neurological Signs.*—They are present in more than one-third of the cases, in the form of paresthesias. They manifest themselves as ticklings, formications, or numbness of the hands.

Very rare are some medullary disorders that resemble the subacute combined degeneration syndrome.[147]

7. *Adynamia and Fatigability.*—These are among the most frequent and the most incommoding signs. These patients are often considered as pithiatics!

8. *The Fall of Serum Iron.*—The signification of the sideremia in iron deficiency was shown by Heilmeyer and Plötner, in 1937; the diminished rate of the circulating iron is the common denominator of all these anemias. It is accompanied by a rise of transferrin and blood copper.

Since Waldenström,[373] hyposiderosis without anemia has been described; it has also been erroneously named "anemia without anemia." It is generally found in women of between 30 and 40 years, with a Plummer-Vinson syndrome and other signs of tissular sideropenia. The red cell count and the hemoglobin level are scarcely altered, although the hyposideremia is considerable. Gastric hypo- or anacidity is a frequent finding.

According to Jasinski,[172] nonanemic cases require a minimal treatment of six weeks, while anemic forms demand at least three to four months.

Rustung [303] and Waldenström even described iron deficiencies that do not provoke a fall in serum iron but that are not less curable by the iron therapy. In these cases, the tissular signs of sideropenia are more faithful witnesses than the laboratory responses.

The iron deficiency is thus a general disturbance, affecting the whole organism. The anemia is only one of its usual aspects. Its repercussions show themselves also in a disorder of the intracellular catalyzing functions. The lack of iron is especially perceived in the organs where the cells are constantly regenerated: the bone marrow and the cutaneous and mucous epithelia. The cytochromes have the same signification for the metabolism of these tissues as hemoglobin for the whole of the body. Vannotti [364] showed, indeed, that in long-standing iron deficiencies the cytochromes decrease as much as hemoglobin.

There is a great theoretical and practical interest in how much asiderosis may resemble certain kinds of avitaminoses of the B group; this certainly is more than a coincidence!

Eventually, it is to be noted, the privation of iron may produce some particular symptoms, as a moderate fever without any infection [286,384] or a purpura and ecchymoses.

Iron Therapy

All disorders caused by the lack of iron vanish with iron therapy. The inhibition of the red cell maturation ceases; the tall erythroblasts disappear from the bone marrow and are replaced by normoblasts. The recovery is announced by a reticulocytic crisis that reaches its maximum five to eight days after the beginning of an intravenous treatment. This phenomenon is so constant that it serves as a test to the value of the medication. It was already known by such authors as Naegeli. The urobilin excretion falls to values inferior to normal.

The hemoglobin level rises the more quickly as iron is given in excess. If normal persons take iron per os, their hemoglobin concentration rises to a maximum after 10 to 12 weeks. Afterward the level decreases, even if the medication is continued.[105] In hypochromic anemias, on the contrary, the hemoglobin curve is much steeper and falls back much later (never before the normal value has been attained). The augmentation of the erythrocyte count begins four to five days after the reticulocytic crisis.[266] While debating the mechanism of the iron absorption, I stressed the rapidity with which the metal may be utilized in sideropenic anemias. These anemias accelerate considerably the intestinal iron resorption, although it is independent on the serum iron level.[88,100,282] In an important number of these patients, achylia diminishes the resorption; it may become negligible. The iron therapy restores both gastric pH and the digestive iron absorption.

In this kind of treatment, the nature of the medicament is of utmost importance; man assimilates iron only if it is bivalent. To avoid the spontaneous oxidation of ferrous salts, it is necessary to combine them with the reducing power of ascorbic acid (vitamin C), so as to obtain a maximal utilization coefficient.[147] All the substances that contain iron in a masked nonionizable form are worthless. Such are chiefly the hematin and hemoglobin preparations, so much in fashion formerly. The enzymatic porphyric iron is not available for the absorption.

The necessarily high doses of iron that should be taken by mouth may cause signs of gastrointestinal irritation: vomiting, diarrhea, or constipation, especially. The metal is to be given by preference only during or immediately after meals. The administration of iron per os, especially of ferrous salts, could be dangerous for young children, where it might provoke digestive and neurological disturbances. The literature even mentions a specific syndrome of accidental ferrous sulfate poisoning of such children.[1] It should be said that the

doses had been excessive and were responsible for extensive necrotizing gastroenteritis.

In general, ferrous sulfate is the most active and deservedly the most used of all iron salts. Among all the preparations, it produces the fewest digestive troubles.[266]

During iron therapy, the sideremia is restored only long after the disappearance of the anemia. It is therefore important not only to give sufficient quantities of the metal but also to continue the treatment for weeks or even months[30] after the apparent healing, so as to permit the constitution of adequate reserves. It happens that the oral iron medication does not give the expected amelioration because it is not absorbed in the digestive tract. This is an indication to use the intravenous way, that often permits a normal recovery of all the digestive functions.

It has been explained before that ionized iron is not utilized in injections because of its high toxicity. The hypothesis has been put forward that the intoxication by these salts was a real poisoning, similar to that of heavy metals. In the mouse, however, dimercaprol (British antilewisite) increases the toxicity of iron, even when the metal is taken by mouth.[223]

Other Antianemic Products

Although other antianemic products cannot cure the iron-deficiency disease, their adjuvant role should not be neglected.

The importance of the vitamins of the B group has already been evoked. I must add that nicotinamide intervenes in the integration of iron in the porphyric cycle; its use is to be recommended along with the other vitamins.

The special place of ascorbic acid merits a particular mention; it is the physiological factor that reduces trivalent iron to ferrous ions. It must be included systematically in every iron therapy.

HCl and pepsin are obviously indicated in case of anacidity.

The influence of *copper* has been studied for many years.[118,128-130,162,163,190,191,304,314,321,332,336] This metal, like iron, intervenes in the process of growth and of tissular respiration.[304] Its activity seems capital for the function of cytochrome oxidase.[321]

Rats or rabbits fed only cow's milk develop a hypochromic anemia that resists iron and responds only to copper (milk is very poor in this metal). At the same time, the animals become very weak. Bennets and Beck (cited by Cartwright[50]) could show that this copper deficiency happens spontaneously in the Australian sheep as an *enzootic ataxia*. A similar affection has been described subsequently in many other parts of the world where the earth contains little copper; it may touch bovines, rats, dogs, hens, and pigs. The deficiency is responsible for demyelinization of peripheral nerves and for an intense hypochromic anemia. On pigs, Cartwright et al.[54,128,190,191] showed that this microcytic anemia is absolutely identical to that of sideropenia: Its hematological characteristics are the same; the serum iron level is lowered but the transferrinemia rises; the digestive iron absorption is reduced; the myelogram presents the same alterations in both deficiencies. There is only one distinctive symptom —the cupremia; it is diminished in copper deficiency and elevated in sideropenia. There is thus no doubt that the privation of copper paralyzes the metabolism of iron.[129] Copper is necessary for the assimilation of iron by the digestive tract, for the removal of the tissue iron, and for its utilization by the bone marrow[250] as well as for the formation of the red cell stroma.[148]

The hypochromic anemia of infants may depend on a relative copper deficiency.[17,50,147,148,314] The misappreciation of this privation is responsible for some therapeutic failures. Moore, for example (cited by Cartwright[50]) describes the extended reticulocytosis following two weeks of iron therapy in children; but the subsequent addition of copper sulfate to the treatment produced a new reticulocytic crisis.

Concerning adults, the copper question is much more debated. Most hematologists

think that the hypochromic microcytic anemia of adults responds conveniently to iron therapy alone. Heilmeyer[147] proceeded to more than 3000 blood copper estimations in cases of anemia and never saw an abnormally low level. Some other observers, nevertheless, told of anemias in adults that resisted iron and could be cured only with a supplement of copper.[50,80,294] This eventuality certainly is very rare.

The action of *cobalt* will be discussed later.

It should finally not be forgotten that the hemoglobin synthesis requires iron—but *proteins* too! Fiessinger studied this particularly in famine edemas and created the notion of *erythroplasmatic anemia*, where the primordial deficiency was protein. Whatever the importance of iron, it is but one of the constituents of the hemoglobin molecule; it could not suffice solely to repair an anomaly that may proceed from other privations.

The *prophylactic ingestion of iron* is of particular importance on four special occasions:

1. During pregnancy and lactation.

2. In artificially nourished nurslings. While cow's milk is richer in minerals than mother's milk, the latter contains three times more iron. The infant's needs increase with growth, as its stores tend to be exhausted; finally, a so-called "phyisological" anemia may supervene between the fourth and the sixth months, that is, before the weaning supplies the required supplement of iron. Iron therapy is the more opportune when birth is more premature, for in this case the stores have been incompletely accumulated and the serum may be abnormally low as early as birth.[2]

3. During children's growth period and chiefly at the moment of girls' puberty.

4. Blood donors are capable of giving harmlessly at most 2 or 2.5 liters of blood a year if they are male, 1.5 liters if they are female.[228] They ought to receive systematically a considerable supplement of iron.

Note on the Serum Iron in Nonsideropenic Anemias

In hemolytic anemias, the serum iron is increased. The experimental proof is furnished in phenylhydrazine intoxications, where the rise of the sideremia begins after three to five hours. The same result is obtained with intravenous injections of distilled water into rabbits.

In pernicious anemia, elevation of the serum iron level proceeds completely from a lack of utilization of iron (the erythropoiesis being greatly slackened) and from its excessive liberation by increased hemolysis. These disorders are responsible for tissular siderosis developing mainly in the spleen. A fall of the sideremia occurs very rapidly after the beginning of the antipernicious treatment, on the second or the third day, sometimes after 24 hours. This lowering is the earliest of all tests, proving the efficiency of the therapy. Before the establishment of the specific medication, the plasma transferrin level is low but the saturation coefficient extremely high; both tend to normal with the treatment.

In aplastic anemias uncomplicated by infections, the sideremia usually is moderately elevated; the catabolism of hemoglobin is normal, but its synthesis, naught.[346]

Even if they depend on an iron deficiency, hypochromic anemias may take various aspects. Some of these will be reviewed in the next pages.

Chlorosis

True chlorosis is an iron-deficiency anemia that, independently of all apparent exogenous causes, supervenes in young girls at puberty. The disease has been rare for 30 or 40 years, though it has not disappeared.

Signs and Symptoms.—They are present in every anemia: palpitations, effort dyspnea, dizziness, ear tinglings, headaches, syncopal attacks, and increased fatigability, with the need of a prolonged sleep.

The psychical character of these patients is such that a confusion with hysteria is not rare.

The pallor of the complexion is striking; it may be greenish in serious cases (whence the name of the disease). An important increase of the stature often precedes the anemia. The menstruations diminish and may even stop completely.

The systematic examination is negative, except for the anemic heart murmurs. Gastric atony and ptosis are frequent. Two particularities are striking:

1. A tendency to edema, conferring a "pasty" aspect to seriously ill persons. Heilmeyer [147] states that extreme cases may have not only anasarca but even cerebral edema with papillary stasis.

2. A propensity to venous thrombosis.

On the contrary, the signs of tissular sideropenia are curiously rare.

The blood film is typical for a hypochromic anemia but not specific for chlorosis. Aside from current anomalies, such as anisocytosis and poikilocytosis, there are witnesses of the disturbance of erythroid regeneration: basophil granulations, normoblasts, and Howell-Jolly bodies. The number of platelets is often increased.

The serum iron is extremely low and never returns to normal before the reparation of the anemia. Iron surcharge curves per os show that the absorption of the metal is very reduced or even completely abolished. After iron therapy, the assimilation acquires, however, incredibly high proportions. There is consequently a trouble of the intestinal permeability to iron, curable only with iron!

Pathogenesis.—Former authors like Naegeli believed in a causative ovarian insufficiency. This opinion is erroneous; the removal of both ovaries never provokes chlorosis, and the illness never is influenced by a corresponding hormonal treatment. The oligomenorrhea is not the cause but the consequence of the lack of iron. The privation directly influences the endocrine glands but perhaps also the neurovegetative system.

Sideropenia alone is responsible for the entire disease, which could be reproduced experimentally in mice and dogs. In these animals even the characteristic fatigue and adynamia appear as well as the absence of estrus.

According to Heilmeyer,[147] the quasispecific genesis of chlorosis in young girls is explained by the concurrence of several causes:

1. The mothers of these adolescent girls frequently suffer a hypochromic anemia; their children do not have sufficient iron stores from their birth on.

2. Growth requires a considerable amount of iron in all tissues. The curve of girls' height increases rises sharply at the menarche, while it is flatter in boys; the iron utilization is consequently still more intense.

3. Menarche provokes, with each bleeding period, a loss of between 25 and 100 mg. of iron. These losses may contribute to rendering the balance of the metal negative.

4. The influence of the alimentation is not negligible. The needs, increased by the preceding factors, normally are compensated by food rich enough in vitamins and iron. For this reason chlorosis is less frequent in war time, when people's aliments are richer in iron than usually (many vegetables, unrefined bread). The alimentary exigencies are but incompletely satisfied in most cases of chlorosis. The estimation of the iron content of these patients' food gives a mean figure of 5.5 mg. a day. This quantity suffices for a normal adult male but is inadequate for a girl at puberty.

5. The present neurovegetative disorders (with or without typical neurosis) should not be neglected. They manifest themselves particularly in the digestive tract, where they cause gastric atony; they certainly inhibit the iron resorption. Their existence gives an easier explanation of the role of physical and psychical stresses, overexer-

tion, mental depression, and "sexual complexes" dear to ancient authors.

Bickel entirely shared Heilmeyer's opinion.

In each particular case of chlorosis, the different factors have a variable importance, one or more of them being primordial.

The actual rarity of the disease finds several explanations. Today the alimentation surely is better balanced for all ages and allows the establishment of convenient iron stores. Besides, the physical and psychical hygiene has been considerably bettered; it does not condemn young girls any more to a sedentary quasi cloistered life.

Forms.—Many forms of chlorosis have been described: masked chlorosis (as we know it now), acute chlorosis of puberty, and tardy chlorosis healing imperfectly or not at all and evolving toward essential chloroanemia.

Diagnosis.—The diagnosis is not always easy; it should eliminate all the other causes that may provoke a hypochromic anemia: tuberculosis, gastroduodenal ulcers, genital or other bleeding, rheumatoid arthritis, nephritis, etc.

Treatment.—The real treatment ought to be prophylactic! Once the disease exists, the patients receive a diet rich in vitamins and proteins but poor in residue so as not to exaggerate the intestinal atony. Iron therapy will begin immediately and be controlled by erythrocyte counts and sideremia determinations.

Posthemorrhage Anemia

In normal men, a bleeding of between 500 and 800 cu. cm. produces a fall in serum iron that exceeds considerably the corresponding lowering of the hemoglobin level; iron is indeed immediately utilized by the bone marrow to repair the anemia. Between 24 and 48 hours later, the sideremia rises, for the stores are released. This augmentation does, however, not take place if the bleeding has been more copious; the iron stores do not suffice any more to compensate the losses.

As in every sideropenic anemia, the blood copper level rises.

The iron deposits will be very rapidly exhausted if the alimentation does not contain much of the metal. This will be realized in diets for digestive disorders and in certain populations (Scandinavians, for example).

The discovery of a hypochromic anemia must incite the immediate research of a chronic bleeding; mostly digestive (ulcer or ulcerations, tumors, hemorrhoids, etc.), its site may be elsewhere: urinary or nasal, for example. In women, a great attention ought to be paid to genital hemorrhages. The anamnesis may neglect neither the duration and the abundance of menstruations nor the particular circumstances that accompanied pregnancies, abortions, deliveries, and lactation.

The treatment of this type of anemia will be double, restoring the iron balance at the same time as it stops the blood loss.

Nutrional Anemias

The iron consummation is increased in three physiological circumstances: during the growth of infants and young children, at the end of the rapid development that coincides with the menarche in girls, and after each menstruation.

In nurslings, the sideropenic anemia occurs especially between 4 months and 4 years. These children often were fed with cow's milk that contains little iron. The anemia is the more frequent as birth was more precocious; the constitution of the stores happens only in the last months of fetal life.

Lato [205,206] found a normal sideremia in breast-fed infants but a lowered serum iron level in nurslings fed with cow's milk. The sideropenic anemia is, however, only one of the aspects of iron deficiency in the young creature; the child's growth is retarded, and it is particularly predisposed to respiratory and digestive disturbances.

As related already, a copper deficiency may complicate the sideropenia.

In adults, the anemias of iron privation are found nearly exclusively in women. Fullerton, Davidson, et al. (cited by Heilmeyer [147]) made very extensive investigations in the indigent population of Scotland. They discovered a frankly insufficient iron content of the alimentation. The hemoglobin level and erythrocyte count of these Scottish women diminish regularly from 20th to the 45th year; the severest anemias are premenopausal, as the foods have not been able to compensate progressive menstrual blood losses.

In males, such anemias are not found, unless in some pathological conditions. The current peptic ulcer diet for instance procures only a few milligrams of iron per day, insufficient to compensate the evident or occult hemorrhages that accompany the affection. A supplement of iron should systematically be given to these patients.

Septuagenarians or octogenarians may present a similar anemia, owing to an unequilibrated alimentation complicated by absorption disorders.

Sideropenic Anemias Proceeding from Digestive Disturbances

Diseases of the gastrointestinal tract never could be responsible for an anemia if there was not a simultaneous iron metabolism alteration—bleeding, lactation, or infection.

1. *Agastric Anemias.*—The agastric anemias have been intimately studied in animals. In man they supervene rarely after gastroenterostomy— more frequently after gastrectomy.[217] Women, of course, are more exposed to it. The anemia has the same outlook as essential hypochromic anemia. It occurs usually a very long time after the operation, a latency of 10 years being no rarity; this duration is in fact necessary to deplete the iron stores.

The cause of the poor iron resorption probably is triple; the anacidity inhibits the ionization of alimentary iron; the acceleration of the transit hinders the absorption; the diet is deficient in iron.

The treatment consists of ionized ferrous salts and supplementary HCl.

2. *Anemia of Gastric Carcinoma.*—This is very frequent. It often has a macrocytic character (This again draws the attention on the importance of the stomach in the genesis of macrocytosis!). Its origin is more complex. The cancer by itself limits erythropoiesis (see below); besides, there is often a chronic blood loss and a profound alteration of the functions of the gastric mucosa. The aberrant iron metabolism in malignant tumors explains why this anemia is refractory to iron therapy, even in very high doses.

3. *Anemias Associated with Diaphragmatic Hernias.*—Although the sideropenic etiology of these anemias leaves no doubt; their pathogenesis is not entirely understood. They complicate nearly 20% of gastric hernias. The bleeding from passive mechanical congestion certainly plays an important role, the only responsible one, according to Mandart and Sonnet. Very probable, however, are associated disorders of the absorption.

These anemias predominate in overweight women aged more than 50. The latent forms of the hernias really are numerous; they are detected only during careful radiological examinations (which are required in all obscure cases of anemia). The anemia itself is not an indication for surgery; the affirmation is unanimous; the operation is indicated in seriously bleeding cases. It is necessary to institute a vigorous iron therapy and to watch the patient closely to avoid any relapse.

Essential Hypochromic Anemia or Essential Chloroanemia

This is an iron-deficiency disease, the fundamental mechanism of which is still unknown. It touches nearly exclusively women of about 40 years. It is curable with iron but does not heal spontaneously; be-

sides, the metal procures only a symptomatic improvement.

The anamnesis of these patients often mentions menorrhagia and/or multiple pregnancies.

Signs and Symptoms.—They are the same as in every iron deficiency but particularly intense. Several complaints evoke Biermer's disease: burning of the tongue, nausea, diarrhea, ticklings, and formications of the hands. The Plummer-Vinson syndrome is frank. As in chlorosis, there is a tendency to edemas that, with the anemic heart murmurs, suggest too easily a cardiac decompensation.

The blood film, identical in all hypochromic anemias, does not allow an etiological diagnosis. Monocytosis is not rare. The sideropenic symptoms are classical on the skin, mucous membranes, nails, and hair. In most cases there is anacidity that often resists to histamine. It disappears after treatment; here, too, it is a consequence but not the cause of the disease.

The surcharge curves per os are flattened, demonstrating thus the trouble of the absorption.

The spleen may be enlarged, without ever acquiring tumoral proportions. Menstrual anomalies are frequent.

In Scandinavian countries, sideropenic dysphagia is twice as frequent as cancer of the esophagus. The Scandinavians eat only feeble quantities of meat and of vegetables and are therefore often in a latent iron-deficiency state.

Diagnosis.—The diagnosis should discard all other possible causes of hypochromic anemia (chronic infections, malignant tumors, chronic bleeding). The age of the patient, the absence of icterus and of megaloblastosis, and the inefficiency of liver therapy allows the exclusion of Biermer's anemia.

The transformation of essential chloroanemia into a pernicious one is perhaps not rare. The two affections are probably allied. Vannotti and Delachaux, like Heilmeyer, believe in the following evolution: The absorption of iron is inhibited first; during the progress of the disease, Castle's factor could become missing. In this case, the symptoms of pernicious anemia predominate over these of the hypochromic one; the latter reappear during the healing of Biermer's disease.

Pathogenesis.—Several elements concur in the advent of the disease (Hallen):

1. There is certainly a familial predisposition, that joins the hereditary character of pernicious anemia and gastric cancer. Some genealogical trees are particularly demonstrative.

2. Sometimes the alimentary intake is insufficient; but there is always an altered intestinal absorption.

3. The importance of gastric anacidity is discussed because badly elucidated. Lederer [211] suspects the absence of a special ferment that separates iron from foods in the stomach; in vivo it liberates the iron content of egg yolk, provided it is placed in an acid pH. Heilmeyer and von Mutius, on the contrary, cannot obtain a better ionization of alimentary iron with gastric juice than with a solution of commercial HCl and pepsin. Minot, Pohle, and Alstedt (cited by Heilmeyer [147]) brought, however, a confirmation to Lederer's opinion. They mixed normal gastric juice with foods rich in iron and administered the mixture to chloroanemic patients; they obtained an improvement. In Dominici's experience, the disease can be cured by the intramuscular injections of neutralized gastric juice of normal persons or even of patients with Biermer's disease.

Essential hypochromic anemia could, therefore, be the consequence of the alteration of a specialized enzyme, impeding thus the normal transformation of iron in the body. This could explain why the iron therapy is only symptomatic.

More recently, Lambin and Lederer estimated that the disease is extremely rare, if it ever exists. They published a series of cases where a careful inquest never failed to reveal a satisfactory explanation

for the iron deficiency. To the classical causes of occult bleeding, they join a rather important number of gastric hiatal hernias, the frequency of which they think underrated. One may object to these authors that their remarks have no real relation with essential chloroanemia as it is unanimously defined.

Treatment.—The only treatment known until now is iron; it is a substitution medication. Great doses of it ought to be administered, amounting to five times the quantities given usually.[147] It will often be necessary to begin treatment with intravenous injections till there is at least partial recovery of the intestinal absorption. In every case, the therapy has to be continued as long as the hemoglobin level does not reach 90% or, better, until the serum iron returns to normal. At this moment a maintenance dose should be continued. The treatment may be definitely interrupted only after menopause, when the iron loss is stopped and its balance, no longer negative.

An *essential hypochromic anemia of pregnancy* has been described. It is entirely similar to the preceding, except that it heals spontaneously after delivery. It is beyond doubt that the great iron spoliation of pregnancy is the major factor in its genesis.

The Anemias of Infection and Malignant Tumors

These anemias belong to a special pathogenetic category, which Wintrobe et al. studied particularly.[386-397]

They are subordinate to an infection or a neoplasm; there is neither bleeding nor exaggerated hemolysis (no jaundice, no hyperbilirubinemia, no elevation of urinary or fecal urobilinogen, except in septicemia or fulminating infections). The destruction of erythrocytes may nevertheless be accelerated, as in leukemias, for instance. No iron is abnormally excreted.

Infection and cancer are the most frequent causes of anemia—50% to 60%.[397] In man, other diseases may provoke an anemia of the same type, though their nature is not really infectious. In rheumatoid arthritis, for instance, the hemoglobin and serum iron levels are in inverse relation to the seriousness of the illness and the sedimentation rate.[38]

Anemias of infection are generally not very grave. Their intensity depends on (*a*) the duration of the causal disease (they are rare before one month; on the other hand, they do not increase continuously but remain stationary after some time); (*b*) the degree of the inflammation.

The disorders of erythropoiesis in infections and malignancies are characterized by a cellular and pigmentary anemia, an alteration of the metabolism of iron and copper, and a disequilibrium of nitrogen balance.

Cellular Anemia.—In the beginning of an infection, reticulocytosis is normal. It diminishes gradually and is followed by a reduction of the erythrocyte count. At a certain moment, however, this hypoplastic phase of the bone marrow gives place to an increase of the reticulocytic number that does not disappear any more (even if the patient does not improve) and that prevents the aggravation of the anemia.[152] This revival of the bone marrow occurs when the hemoglobin level descends under a threshold value of 65% to 50% of normal.

Pigmentary Anemia.—Reduction of the Hemoglobin Level: After injection of iron isotopes into normal men or animals, 24 hours suffice for the production of "marked" red cells, the number of which increases during two or three weeks; 80% of the injected iron is utilized to this end.[397] In infectious anemia, the uptake is considerably diminished. It begins much later[403] and the degree of iron integration in the erythrocytes seems inversely proportional to the severity of the infection.

The hindrance to the hemoglobin synthesis explains the increase in free protoporphyrins in erythrocytes and urine (Type III, No. 9). If this increase attains its maximum with the acme of the anemia, the free protoporphyrin disappears only long

after the healing of the anemia. Its elevation is related to the duration of the infection—less to the degree of the anemia. It means that the protoporphyrin synthesis is normal but that its transformation in hemoglobin is slackened. As in sideropenic anemias, the reaction

$$Fe + \text{protoporphyrin} \longrightarrow \text{heme}$$

is greatly delayed and leaves an excess of the porphyrin reagent in the red cells.[386]

The anemia is of a normocytic normochromic or moderately hypochromic type.

Iron Metabolism.—The modifications of iron metabolism are profound. Sideremia is constantly lowered during inflammations, in direct proportion to hyperpyrexia. It returns to normal only after complete recovery and when the anemia has completely vanished. Vannotti and Delachaux followed this in pulmonary tuberculosis. They found that cases with a poor defense against the respiratory infection had a very low sideremia; the serum iron level was but little lowered in chronic forms of the disease. Parella and Rescigno confirm these results but do not find a statistical correlation between the activity of the tuberculous process and the fall of serum iron.

During infections, the reticuloendothelial system proliferates considerably. At the same time, it attracts avidly the circulating iron. The metal accumulates thus within this tissue, where it may become microscopically visible (liver, spleen, bone marrow, and lymph nodes). The liver is principally responsible for this embezzlement; in chronic inflammations, the proportions of iron in blood and hepatic tissue are inversely correlated.

This forestalling takes place to the prejudice of erythropoiesis. Its exact significance is not yet clear. It is a part of the defense mechanisms that the reticuloendothelial system opposes to inflammation and for which iron seems indispensable. Hettche (cited by Vannotti [365]) obtained, indeed, a longer survival if animals, inoculated with diphtheria, received supplementary iron; their general status improved and the infection became less severe.

After the healing of inflammation, the stored iron is put at the disposal of the bone marrow. At this moment, the serum iron level may rise transitorily above normal. This is the case in dogs after the closing of Staphylococcus abscesses.

Todt could show a narrow correlation between sideremia, temperature, and sedimentation rate in man, even in malaria (notwithstanding the exaggerated hemolysis in this illness).

Twenty-four hours after the injection of typhoid vaccine in normal subjects, the serum iron decreases; its level rises to normal after one day. If the inflammation is maintained for a longer time, the hyposideremia persists. Anemia, however, does not supervene before long and only if the inflammation is sufficiently severe during a sufficiently long time. In dogs bearing staphylococcic abscesses, the fall of serum iron also precedes anemia by a long time.

Not only do septic inflammations produce a decrease of circulating iron, but also experimental sterile turpentine abscesses, injections of histamine, epinephrine, horse's serum, corticotropin, and cortical extracts. If the animals' reticuloendothelial system has been blocked previously with colloidal thorium dioxide, all these substances have no more effects on the iron metabolism; this demonstrates that the reticuloendothelial tissue is the common executor of these effects. The explanation of these phenomena is difficult. Stress is certainly associated with a fall of serum iron. Feldthusen [95] followed patients during their stay in different surgical wards. Every major operation consistently lowered the sideremia, and its restoration required at most 12 days. If the operation was a minor one, the iron concentration suffered nearly no alteration. Other stresses, too, provoke a lowering of sideremia—the acute phase of myocardial infarction, for instance, where the persistence of a low value is of bad omen.[251]

Hyposideremia also occurs in traumatic shock.[96,397]

It has been stated that adrenal hormones play an important role in this type of hyposideremia. In their operated-on patients, Feldthusen et al. discovered an eosinopenic reaction simultaneous with the fall of serum iron; the day following the intervention, the excretion of 17-ketosteroids was lessened but that of 11-oxysteroids was increased. There is nevertheless an objection: Addison patients, too, have a stress hypoferriemia![204] The reticuloendothelial activity might thus partially be determined by the adrenals. It was tempting to postulate that inflammation, acting like a stress, excites the adrenals and, through them, stimulates the reticuloendothelial tissue that captates iron from the serum. However, appealing this theory may seem, there are several serious objections:

(*a*) In man, corticotropin and corticoid hormones do not invariably produce a fall of serum iron.

(*b*) Experiences with rats could not prove a clear relation between adrenals and sideremia. Feldthusen could not show a correlation between phenomena depending directly on the suprarenal cortex (eosinopenia, for example) and the fall of serum iron. One could not support the regulation of all reticuloendothelial activities by the adrenals.

(*c*) Nothing substantiates that those glands have an exaggerated function in chronic infections; no argument exists to demonstrate that a modification of their secretions alters the iron metabolism in an exclusive way.

Certain other factors partake definitely of the fall of the sideremia. The oral iron-tolerance curves are very flat in chronic infections, owing either to a diminution of digestive absorption or to an accelerated departure of iron from the plasma or even to both these possibilities.

1. The digestive iron absorption surely is slackened. Wintrobe[388] administered radioactive iron to rats; while normal animals take up 22% of it, rats bearing staphylococcic or turpentine abscesses absorb less. During the growth period of young animals, the total iron of the body increases in a slower way if they suffer from a chronic infection.

Schäfer[309] tried the balance technique in infected children and concluded an augmented resorption. One should object that balance calculations are very delicate and frequently tainted with errors.

2. During chronic inflammations, an intravenous iron injection produces a maximal hypersideremia after five minutes, i. e., as normally. The level falls, however, to its initial low value after 3 to 5 hours, the normal duration of this hypersideremia being between 8 and 12 hours. This capture of iron from the plasma is so intense that it perseveres even after intravenous injections of colossal quantities of colloidal iron saccharate.[386]

Inflammation has accordingly the power of reducing both the digestive absorption of iron and its persistence in the circulation.

The transferrin concentration falls, too, but less than the sideremia, so that the saturation coefficient also diminishes. The lowering of both total iron-binding capacity and serum iron results from two independent processes:

(*a*) The intravenous injection of siderophilin to two chronically infected patients raises the transferrin level to normal but is unable to modify sideremia.[392]

(*b*) The injection of typhoid vaccine lowers serum iron but does not alter transferrin concentration. In experimental infections, hyposideremia always precedes the reduction of the siderophilin level.

There is no correlation between the gravity of the anemia, the degree of hyposideremia, and the reduction of the serum iron-binding capacity.

Cohn (cited by Cartwright[397]) discovered abnormal liver protein that may attract the transferrin iron. A functional or ponderal

increase of this protein has not been described until now in inflammation.

The *blood level of copper* rises; it becomes normal again at the same time as the disappearance of the anemia and before the restoration of the sideremia. This hypercupremia occurs before the establishment of the anemia. Its signification, as well as the origin of the copper excess and its role in the infection, is unknown till now.

Protein metabolism is perturbed. Every infection elevates the urinary excretion and renders the nitrogen balance negative. This process is nevertheless self-limited; when the nitrogen losses have been excessive, they abate and finally the balance becomes positive again.

Infected patients keep, however, the capacity of synthetizing their proteins, provided that an adequate amount of raw materials is furnished by the foods and absorbed in the digestive tract. Parenteral supplements of proteins are, on the other hand, not able to correct the anemia of infection.[397] Pigs may develop anemia when given a diet deficient in proteins; they do present neither hyposideremia nor hypercupremia nor an increase in free erythrocyte protoporphyrin.

The disturbances of nitrogen metabolism are nevertheless so important that a protein alteration almost surely partakes of the anemia, even if this participation could not yet be frankly demonstrated.

In malignant tumors, the phenomena are similar to those of infection; the cancers are responsible for an identical profound perturbation of iron metabolism. The digestive absorption of iron diminishes; the metal leaves the blood stream for the reticuloendothelial system with abnormal speed; the transferrin level falls, as well as its saturation coefficient. Hemoglobin synthesis is impeded by a slackening of the iron-protoporphyrin combination and by a difficulty in globin elaboration. Except for occult bleeding complications, these tumor anemias never reach a dangerous degree. Their appearance may be a compensation for other highly active processes, such as defense mechanisms, the importance of which primes the erythropoietic necessities.

Treatment.—The considerable augmentation of tissular metabolism requires of course an intense enzymatic activity and thus probably a supplement of iron. With iron therapy, Vannotti and Delachaux believe they can ameliorate the general status of their patients and even the causative infection.

Wintrobe's group has a completely opposite opinion; great quantities of iron administered to their patients did not have any beneficial effect. Tötterman also did not see, on the hemoglobin level or the erythrocyte number, any influence of important doses of intravenous iron, amounting to even 1.342 mg. The abnormal behavior of iron during infections explains the failure of this kind of treatment.

The only valuable medication is that which suppresses the consequences of inflammation; corticotropin and cortisone may do so. Their favorable effects, not only in infections but also in other inflammations, such as rheumatoid arthritis, have been sufficiently described. The anemia by itself, however, does not justify their use!

Liver extracts, copper, iron ascorbate, and ascorbic acid are devoid of any influence on the erythrocyte perturbation.[356]

Recently, several authors stressed the value of *cobalt* in the treatment of anemia, even when of infectious origin.[81,93,108,157,180,183,292,298,299,377,381,391,394] It is independent of the action of cyanocobalamin cobalt. Pitini and Messina (cited by Hendrych [157]) established the rise in hemoglobin after the administration of cobalt in 1899. Waltner and Waltner first used this property in practical medicine.

The metal announces its effects with a reticulocytic crisis. Its use may lead to an experimental polycythemia. According to Kleinberg et al., it represents the most powerful erythropoietic that we dispose of. In bled rabbits, its use allows the regeneration of the lost red cells in half the time

necessary to control animals; the first lot is already polycythemic, while the second only arrives at recovery. Cobalt also impedes the development of benzol anemia in laboratory animals.

During cobalt treatment, the bone marrow forms great polylobulated cells that Kleinberg interpretes as erythropoietic megacaryocytes. Weissbecker confirms this picture.

In herbivorous animals, a deficiency in cobalt provokes a disease first described in New Zealand and called "bush sickness," "coast disease," or "enzootic marasmus." Its main symptoms are severe anemia, identical to sideropenic anemia, and a progressive emaciation.

Man's daily requirements could amount to 30 mg.[298]

Numerous experiences confirmed the results of cobalt therapy in normal animals as well as in infections. The administration of cobalt constantly lowers the serum iron level[299] but raises the hemoglobin concentration, and (after a reticulocytosis about the sixth day) the erythrocyte number eventually reaches that of polyglobulism. These figures are transitory and cease two to three weeks after the suppression of the medication.

Without a sufficient amount of iron and copper, the metal is powerless.[157,391]

Identical results are obtained in man. On the fifth day the number of the red corpuscules has already increased.[381] A treatment of four weeks' duration may produce a daily elevation of 100,000 or 200,000 erythrocytes per cubic millimeter and of 3% to 5% hemoglobin, thus ending with real polyglobulism. There is no change in the leukocyte count or formula. Serum iron levels are constantly lowered. After cessation of the treatment, all these values come back to normal.

The anemia of chronic renal diseases regresses in a series of Gardner's cases.

The mechanism of action of the metal is imperfectly understood. Griffith et al. found they could prevent every effect of cobalt by simultaneous administration of sulfhydryl-containing amino acids (choline, methionine cystine, and cysteine). They postulate that cobalt blocks the intracellular sulfhydryl groups and thus inhibits the cellular oxidoreduction. The tissular anoxia that results should stimulate the erythropoiesis in the bone marrow. Ascorbic acid, too, impedes the action of cobalt.[298,381]

In practice, there is a contraindication to use of the product in hepatic or biliary disorders (the metal being excreted by the liver), as well as in severe renal disorders.

Waltner and Waltner, Kato, Wintrobe et al., and Gardner give cobaltous chloride or sulfate in amounts of 20 to 100 mg. a day. The medicament may produce anorexia, nausea, and vomiting, but the secondary effects are suppressed by enclosing the drug in glutenized capsules.

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REFERENCES

1. Acute Iron Poisening, Editorial, Nutrition Rev. 10:299, 1952.

2. Albers, H.: Eisen bei Mutter und Kind, Leipzig, VEB Georg Thieme, 1941.

3. Alsted, G.: Chlorosis: Essential Juvenile Iron Deficiency Anemia, Am. J. M. Sc. 201:1, 1941.

4. Andersson, N.: Experimental and Clinical Investigations into the Effect of Parenterally Administered Iron, Acta med. scandinav., Vol. 138, Supp. 241, 1950.

5. Apperly, F. L.: Ionic Concentration of Gastric Juice Following Changes in Red Cell Content of the Blood, Am. J. Digest. Dis. 21:93, 1954.

6. Apperly, F. L., and Cary, M. K.: Relation of Gastric Acidity to Erythrocyte Content of Blood, Am. J. Digest. Dis. 3:466, 1936.

7. Apperly, F. L. and Crabtree, M. G.: Relation of Gastric Function to Chemical Composition of Blood, J. Physiol. 73:331, 1931.

8. Arendsen de Wolff-Exalto, E.: Further Investigations on Influence of Sex Hormones on Blood Picture, Arch. internat. pharmacodyn. et thérap. 74:301, 1947.

9. Arnold, O., et al.: Über die Wirkung des Follikelhormons auf Knochenmark und Blut bei Hunden, Arch. exper. Path. u. Pharmakol. 186:1, 1937.

10. Arvy, L.; Gabe, M., and Stutinsky, F.: Hypophyse et hématopoïèse: I. Le Retentissement de l'hypophysectomie sur l'hématopoïèse du rat albinos, Rev. hémat. 3:154, 1948.

11. Aschkenasy, A.: Maladies des globules rouges et désordres endocriniens: Le Rôle des glandes endocrines dans l'érythropoïèse, Sang 23:89, 1952.

12. Aschkenasy, A.: Données actuelles sur le rôle des protéines dans la formation des cellules sanguines, in Symposium sur la biochimie de l'hématopoïèse, Paris, Masson & Cie, 1952.

13. Aschkenasy, A., and Renier, E.: Etudes cliniques sur les variations du fer sérique et de l'absorption digestive du fer sous l'effet de l'ACTH et de la cortisone, Sang 25:31, 1954.

14. Aschner, B.: Über die Funktion der Hypophyse, Arch. ges. Physiol. 146:1, 1912.

15. Atzmon, A., Szejnberg, A., and Munfred, D.: The Value of Serum Iron Estimation in the Differential Diagnosis of Obstructive Jaundice and Infectious Hepatitis, Harefuah 48:146, 1955; abstracted, Deutsche med. Wchnschr. 80:1206, 1955.

16. Austoni, M. E.; Ziliotto, D., and Odeblad, E.: Thyroid and Iron Metabolism, Acta med. Scandinav. 155:329, 1956.

17. Axtrup, S.: The Blood Copper in Anaemias of Children, Acta pædiat. (Supp. 1) 35:198, 1948.

18. Baez, S.; Mazur, A., and Shorr, E.: Role of Neurohypophysis in Ferritin-Induced Antidiuresis, Am. J. Physiol. 169:123, 1952.

19. Baldini, M., and Mauri, C.: Experimentelle Untersuchungen über die Existenz eines myelotropen Hormons der Schilddrüse, Acta haemat. 10:1, 1953.

20. von Balo, J., and Pubjesz, B.: Über die Wirkung des Follikelhormons, Klin. Wchnschr. 16:1150, 1937.

21. Bateman, J. C.; Klopp, T. C., and Miesfeld, P.: Serum Iron Response to Pituitary Adrenal Agents in Normal and in Cancer Patients, Blood 7:1093, 1952.

22. Beer, A. G.: Untersuchungen über die Regulation des roten Blutbildes, Verhandl. deutsch Gesellsch. inn. Med., Kong. 51, p. 399, 1939.

23. Beer, A. G., and Bedacht, G.: Nebenniere und Blutregulation, Klin. Wchnschr. 20:1000, 1941.

24. Beer, A. G., and Bedacht, G.: Untersuchungen über die Reaktionsfähigkeit der blutbildenden Organe nach Splanchnicusdurchschneidung, Klin. Wchnschr. 20:1048, 1941.

25. Begg, R. W.: The Modification of Tumour-Host Relations by Steroid Hormones, in Ciba Foundation Colloquia on Endocrinology: Vol. 1. Steroid Hormones and Tumour Growth and Steroid Hormones and Enzymes, edited by G. E. W. Wolstenholme, London, J. & A. Churchill, Ltd., 1952, p. 170.

26. Belsasso, E., and Zucconi, V.: Le alterazioni del ricambio del ferro nello scompenso cardiaco, Rass. giuliana med. 7:147, 1951.

27. Benda, L.; Rissel, E., and Scholda, G.: Zur Frage des Eisenstoffwechsels bei der akuten Hepatitiden, Wien. klin. Wchnschr. 63:794, 1951.

28. Berlin, N. I.; Van Dyke, D. C.; Siri, W. E., and Williams, C. P.: Effect of Hypophysectomy on Total Circulating Red Cell Volume of Rat, Endocrinology 47:429, 1950.

29. Betz, H.: Recherches expérimentales sur les fonctions cortico-surrénaliennes et l'hématopoïèse, Ann. endocrinol. 12:801, 1951.

30. Beutler, E.; Drennan, W., and Block, M.: The Bone Marrow and Liver in Iron-Deficiency Anemia: Histopathologic Study of Sections with Special Reference to Stainable Iron Content, J. & Clin. Med. 43:427, 1954.

31. Bickel, G.: La Physiopathologie du fer et la thérapeutique martiale, Première Journée de Thérapeutique Clinique Organisée par la Clinique Thérapeutique Universitaire de Genève, 21 Octobre 1943, Geneva, A. Skirka, 1946.

32. Bilger, R., et al.: Blutbild- und Serumeisenuntersuchungen bei sportlicher Höchstbelastung, Deutsche med. Wchnschr. 79:1339, 1954.

33. Bonvallet, M.; Morel, E., and Thiery, G.: Modifications sanguines permanentes observées à la suite de lésions de l'hypothalamus antérieur, chez le chien, compt. rend. Soc. biol. 145:381, 1951.

34. Bothwell, T. H.; van Doorn-Wittkampf, H. V.; Du Preez, M. L., and Alper, T.: The Absorption of Iron: Radioiron Studies in Idiopathic Hemochromatosis, Malnutrition Cytosiderosis, and Transfusional Hemosiderosis, J. Lab. & Clin. Med. 41:836, 1953.

35. Bothwell, T. H.; Hurtado, A. V.; Donohue, D. M., and Finch, C. A.: Erythrokinetics: IV. The Plasma Iron Turnover as a Measure of Erythropoiesis, Blood 12:409, 1957.

36. Boulin, R., and Bamberger, J.: L'Hémochromatose familiale, Semaine hôp. Paris 29:3153, 1953.

37. Brand, M.: Effect of Estrogens on Production of Reticulocytes, Acta brev. Neerland. 15:20, 1947.

38. Brendstrup, P.: Serum Copper, Serum Iron and Total Iron-Binding Capacity of Serum in Patients with Rheumatoid Arthritis, Copenhagen.

39. Brendstrup, P.: Serum Iron, Total Iron-Binding Capacity of Serum, and Serum Copper in Normals, Scandinav. J. Clin. & Lab. Invest. 5:312, 1953.

40. Brendstrup, P.: Serum Iron, Total Iron-Binding Capacity of Serum and Serum Copper in Acute Hepatitis, Acta med. scandinav. 146:107, 1953.

41. Brøchner-Mortensen, K., and Olsen, C.: Colorimetric method for the Determination of Iron in Serum, Compt. rend. trav. lab. Carlsberg, série chim. 23:235, 1940.

42. Brückel, K. W.: Über die Bedeutung von Spurenelementen in der Leber, Deutsche med. Wchnschr. 80:1612, 1955.

43. Bruckel, K. W.; Pietzonka, H., and Pfeilsticker, K.: Zur Klinik und Histochemie des Eisenstoffwechsels der Leber, Deutsche. med. Wchnschr. 81:132, 1956.

44. Brügel, H., and Pietzonka, H.: Mangelernährung und Eisenablagerung in der Leber, Deutsche med. Wchnschr. 80:1002, 1955.

45. Büchmann, P.: Die Bedeutung der Serumeisenbestimmung für die Klinik, Ergebn. inn. Med. u. Kinderh. 60:446, 1941.

46. Cardini, G., and Verrotti, M.: Ricerche sulla regolazione endocrina dell'ematopoiesi: Stato attuale della questione e piano delle recerche, Clin. pediat. 32:596, 1950.

47. Carey, N.: The Effect of Crude Anterior Preparation on Haemopoiesis in Normal, Thyroidectomized and Gonadectomized Rats, J. Clin. Endocrinol. 10:836, 1950.

48. Carnot, P., and Deflandre, O.: Sur l'Activité hémopoïetique du sérum au cours de la régénération du sang, Compt. rend. Acad. sc. 143:384, 1906.

49. Carnot, P., and Deflandre, O.: Sur l'Activité hémopoïetique des différents organes au cours de la régénération du sang, Compt. rend. Acad. sc. 143:432, 1906.

50. Cartwright, G. E.: Dietary Factors Concerned in Erythropoiesis, Blood 2:111 and 256, 1947.

51. Cartwright, G. E.: Studies on the Iron-Binding Capacity of Serum, in Symposia on Nutrition of the Robert Gould Research Foundation, 1947: Vol. I. Nutritional Anemia, Cincinnati, The Robert Gould Research Foundation, Inc., 1947, p. 116.

52. Cartwright, G. E., et al.: Studies on Free Erythrocyte Protoporphyrin, Plasma Iron and Plasma Copper in Normal and Anemic Subjects, Blood 3:501, 1948.

53. Cartwright, G. E., et al.: The Role of the Adrenal Cortex in the Regulation of the Plasma Iron Level and the Functional State of the Reticulo-Endothelial System, in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, New York, The Blakiston Company (division of McGraw-Hill Book Company, Inc.), 1951, Vol. 1, p. 405.

54. Cartwright, G. E.; Gubler, C. J.; Lahey, M. E., and Chase, M. S.: On The Relation of Copper to the Metabolism of Iron, J. Clin. Invest. 31:620, 1952.

55. Cartwright, G. E.; Gubler, C. J., and Wintrobe, M. M.: Studies on Copper Metabolism: XI. Copper and Iron Metabolism in the Nephrotic Syndrome, J. Clin. Invest. 33:685, 1954.

56. Chaloupka, M.; Leverton, R. M., and Diedrichsen, E.: Serum Iron and Hemoglobin Values of 275 Healthy Women, Proc. Soc. Exper. Biol. & Med. 77:677, 1951.

57. Christian, E. R.: Behavior of Serum Iron in Various Diseases of the Liver, A. M. A. Arch. Int. Med. 94:22, 1954.

58. Cohn, E. J.: The Chemical Specificity of the Interaction of Diverse Human Plasma Proteins, Blood 3:471, 1948.

59. Contopoulos, A. N., et al.: Increase in Circulating Red Cell Volume After Oral Administration of Pituitary Anterior Lobe, Blood 8:131, 1953.

60. Cook, S. F., and Spilles, N. M.: Some Factors Regulating the Utilization of Splenic Iron, Am. J. Physiol. 98:626, 1931.

61. Copper and Iron Metabolism, Editorial, Nutrition Rev. 11:336, 1953.

62. Crafts, R. C.: The Effect of Endocrines on the Formed Elements of the Blood, Endocrinology 29:596, 1941.

63. Crafts, R. C.: Effects of Iron, Copper and Thyroxin on Anemia Induced by Hypophysectomy in Adult Female Rat, Am. J. Anat. 79:267, 1946.

64. Crafts, R. C.: Effects of Hypophysectomy, Castration and Testosterone Propionate on Hemopoiesis in the Adult Male Rat, Endocrinology 39: 401, 1946.

65. Crafts, R. C.: Effects of Estrogens in Bone Marrow of Adult Female Dogs, Blood 3:276, 1948.

66. Crafts, R. C.: Effects of High Protein Diet on the Anemia Induced by Hypophysectomy in Adult Female Rats, Including Further Details on Posthypophysectomy Anemia, Endocrinology 45: 159, 1949.

67. Crafts, R. C., and Walker, R. S.: Effects of Hypophysectomy on Gastric Acidity of Adult Female Rats, Endocrinology 40:395, 1947.

68. Crafts, R. C., and Walker, R. S.: Effects of Hypophysectomy on Serum and Storage Iron in Adult Female Rats, Endocrinology 41:340, 1947.

69. Crafts, R. C., and Meineke, H. A.: Presence of Erythropoietic Factor in Plasma of Normal and Hypophysectomized Rats Following Bleeding, Proc. Soc. Exper. Biol. & Med. 92:222, 1956.

70. Dagnelie, J.: Remarques relatives au métabolisme du fer, Acta gastro-enterol. belg. 14:545, 1951.

71. Dahl, S.: Serum Iron in Normal Women, Brit. M. J. 1:731, 1948.

72. Damm, G.; Hammer, F., and Pretzsch, W.: Das "Basis-EKG" (Nacht-EKG): Seine Erkennung und diagnostische Bedeutung, Deutsche med. Wchnschr. 80:41, 1955.

73. Darby, W. J.: Iron and Copper, Council on Foods and Nutrition, J. A. M. A. 142:1288, 1950.

74. Darby, W. J., et al.: The Absorption of Radioactive Iron by Children 7-10 Years of Age, J. Nutrition 33:107, 1947.

75. Daughaday, W. H.; Williams, R. H., and Daland, G. A.: The Effect of Endocrinopathies on the Blood, Blood 3:1342, 1948.

76. Daum, S.: Plasma Copper and Plasma Iron Levels in Diseases of the Thyroid Gland, Biol. listy 32:29, 1951.

77. Davis, W. D., Jr., and Arrowsmith, W. R.: The Treatment of Hemochromatosis by Massive Venesection, Ann. Int. Med. 39:723, 1953.

78. de Duve, C., and Vuylsteke, C. A., cited by Hedon, L.: Certitudes et hypothèses sur les fonctions du pancréas, Montpellier méd. 44:301, 1953.

79. Dejardin, J., and Lambrechts, A.: Recherches sur le taux de fer plasmatique de l'adulte, Acta biol. belg. 2:159, 1942.

80. de Vries, S. I.: De betekenis van koper bij de behandeling van tegen ijzer refractaire hypochrome anaemie, Nederl. tijdschr. geneesk. 96:611, 1952.

81. Dittrich, H.: Die Wirkung kleinster Kobaltgaben auf Blutbildung und Eisenstoffwechsel, Deutsche med. Wchnschr. 78:1658, 1953.

82. Dodds, E. C.; Hills, G. M.; Noble, R. L., and Williams, P. C.: The Posterior Lobe of the Pituitary Gland: Its Relationship to the Stomach and to the Blood Picture, Lancet 1:1099, 1935.

83. Dodds, E. C.; Liu, S. R., and Noble, R. L.: Water Balance and Blood Changes Following Posterior Pituitary Extract Administration, J. Physiol. 94:124, 1938.

84. Dominici, G.; Oliva, G., and Tramontana, C.: Die Pathogenese und Therapie der essentiellen hypochromen Anämie, Deutsche med. Wchnschr. 80:883, 1955.

85. Donner, L., and Daum, S.: Serum Iron and the Total Iron Binding Capacity of the Human Serum for Iron in Some Pathological States, Časop. lék. česk. 91:393, 1952; abstracted, Blood 8:188, 1953.

86. Dougherty, T. F., and White, A.: Influence of Hormones on Lymphoid Tissue Structure and Function: The Rôle of the Pituitary Adrenotrophic Hormone in the Regulation of the Lymphocytes and Other Cellular Elements of the Blood, Endocrinology 35:1, 1944.

87. Dreyfus, J. C., and Schapira, G.: Le Fer sérique, Sang 20:374, 1949.

88. Dubach, R.; Callender, S. T. E., and Moore, C. V.: Iron Transportation and Metabolism: Absorption of Radioactive Iron in Patients with Anemia of Varied Etiology, Blood 3:526, 1948.

89. Ducci, H.; Spoerer, A., and Katz, R.: Serum Iron in Liver Disease, Gastroenterology 22:52, 1952.

90. Eckerström, S.: Recherches sur le fer du sérum chez les vieillards, spécialement par rapport aux ulcères chroniques des jambes, Acta med. scandinav. 118:69, 1944.

91. Erslev, A.: Humoral Regulation of Red Cell Production, Blood 8:349, 1953.

92. von Falkenhausen, M.: Über die Wirkung der Kastration auf die Funktion des Knochenmarkes, Arch. exper. Path. u. Pharmakol. 103:127, 1924.

93. Falzoi, M., and Gelati, M.: Sull'azione antianemica del cobalto: II Trattamento con $CoCl_2$ nelle anemie neoplastiche, Gior. clin. med. 33:819, 1952.

94. Feigin, W. M., and Gordon, A. S.: Influence of Hypophysectomy on the Hemopoietic Response of Rats to Lowered Barometric Pressures, Endocrinology 47:364, 1950.

95. Feldthusen, U.; Larsen, V., and Lassen, N. A.: Serum Iron and Operative Stress, Acta med. scandinav. 147:311, 1953.

96. Feldthusen, U., and Lassen, N. A.: Serum Iron After Coronary Occlusion and Traumatic Injuries, Acta med. scandinav. 150:53, 1954.

97. Feuchtinger, O.: Schilddrüse, Ovarium und Blutbildung, Ztschr. ges. exper. Med. 112:55, 1943.

98. Fiessinger, N.: Clinique et investigations, Paris, Masson & Cie, 1946.

99. Finch, C. A.; Gibson, J. G., II; Peacock, W. C., and Fluharty, R. G.: Iron Metabolism: Utilization of Intravenous Radioactive Iron, Blood 4:905, 1949.

100. Finch, C. A., et al.: Iron Metabolism: Pathophysiology of Iron Storage, Blood 5:983, 1950.

101. Fineberg, R. A., and Greenberg, D. M.: Ferritin Biosynthesis: Crystallization of Guinea Pig Ferritin, J. Biol. Chem. 214:91, 1955.

102. Flaks, J.; Himmel, I., and Zlotnik, A.: Sur l'Existence d'une hormone hémopoiétique dans l'hypophyse, Presse méd. 45:1261, 1937.

103. Flaks, J.; Himmel, I., and Zotnik, A.: La Polyglobulie provoquée par les extraits du lobe antérieur de l'hypophyse prouve l'existence d'une hormone hémopoietique, Presse méd. 46:1506, 1938.

104. Forrattini, C., and Selmi, W.: La sideremia nell'ipertiroidismo, Folia endocrinol. 3:869, 1950.

105. Fowler, W. M., and Barer, A. P.: Some Effects of Iron on Hemoglobin Formation, Am. J. Med. Sc. 201:642, 1941.

106. Fowler, W. M., and Barer, A. P.: Plasma Iron: Normal Values; Response Following Medication, Am. J. Med. Sc. 223:633, 1952.

107. Fried, W.; Plzak, L.; Jacobson, L. O., and Goldwasser, E.: Erythropoiesis: II. Assay of Erythropoietin in Hypophysectomized Rats, Proc. Soc. Exper. Biol. & Med. 92:203, 1956.

108. Frost, D. V.; Spitzer, E. H.; Elvehjem, C. A., and Hart, E. B.: Some Effects of Cobalt and Liver Substance on Blood Building in Dogs, Am. J. Physiol. 134:746, 1941.

109. Garcia, J. F.: Unpublished data, cited by Lawrence, J. H.; Berlin, N. I., and Huff, R. L.: Nature and Treatment of Polycythemia: Studies on 263 Patients, Medicine 32:323, 1953.

110. Garcia, J. F., et al.: Increase in Circulating Red Cell Volume of Normal and Hypophysecto-

mized Rats After Treatment with ACTH. Proc. Soc. Exper. Biol. & Med. 76:707, 1951.

111. Gardner, F. H.: The Use of Cobaltous Chloride in the Anemia Associated with Chronic Renal Disease, J. Lab. & Clin. Med. 41:56, 1953.

112. Gillman, J., and Gillman, T.: Structure of the Liver in Pellagra, Arch. Path. 40:239, 1945.

113. Gillman, J., and Gillman, Th.: The Pathogenesis of Cytosiderosis (Hemochromatosis) as Evidenced in Malnourished Africans, Gastroenterology 8:19, 1947.

114. Ginzberg, R., and Heilmeyer, L.: Über die zentralnervöse Regulation des Blutes, Arch. Psychiat. 97:719, 1932.

115. Gitlow, S. E.; Beyers, M. R., and Colmore, J. P.: Metabolism of Iron: II. Intravenous Iron Tolerance Tests in Laennec's Cirrhosis, J. Lab. & Clin. Med. 40:541, 1952.

116. Glatzel, H.: Ernährungskrankheiten, in Handbuch der inneren Medizin, edited by G. von Bergmann, W. Frey, and H. Schwiegk, Berlin, Springer-Verlag, 1954, Vol. 6, p. 532.

117. Gley, P.: Nouvelles Recherches sur l'hématopoïétine, Bull. Acad. nat. méd. 138:435, 1954.

118. Gley, P., and Delor, J.: Sur quelques Propriétés physicochimiques de l'hématopoïétine, Compt. rend. Soc. biol. 149:635, 1955.

119. Gonnermann, W.: Klinischer Beitrag zum Problem der hormonal bedingten Blutarmut, Deutsche med. Wchnschr. 64:1140, 1938.

120. von Gorka, T.: Die Wirkung des Insulins auf die Reticulocytenzahl, Wien. med. Wchnschr. 93:412, 1943.

121. Govaerts, J., and Lambrechts, A.: Interaction in vitro du radiofer du plasma avec le fer des globules rouges, Acta biol. belg. 3:209, 1943.

122. Granick, S.: Ferritin: IX. Increase of the Protein Apoferritin in the Gastro-Intestinal Mucosa as a Direct Response to Iron Feeding, J. Biol. Chem. 164:737, 1946.

123. Granick, S.: Iron Metabolism and Hemochromatosis, Bull. New York Acad. Med. 25:403, 1949.

124. Granick, S.: Metabolism of Some Metals Concerned in Hematopoiesis, in Symposium sur la biochimie de l'hématopoïèse, Paris, Masson & Cie, 1952.

125. Granick, S.: Iron Metabolism. Bull. New York Acad. Med. 30:81, 1954.

126. Greenberg, G. R., and Wintrobe, M. M.: A Labile Iron Pool, J. Biol. Chem. 165:397, 1946.

127. Griffith, W. H.; Pavcek, P. L., and Mulford, D. J.: The Relation of Sulfur Amino Acids to the Toxicity of Cobalt and Nickel in Rats, J. Nutrition 23:603, 1942.

128. Gubler, C. J., et al.: Rôle of Copper in Erythropoiesis, Fed. Proc. 11:445, 1952.

129. Gubler, C. J., et al.: Studies on Copper Metabolism: III. The Metabolism of Iron in Copper Deficient Swine, Blood 7:1075, 1952.

130. Gubler, C. J.; Lahey, M. E.; Cartwright, G. E., and Wintrobe, M. M.: Studies on Copper Metabolism: IX. The Transportation of Copper in Blood, J. Clin. Invest. 32:405, 1953.

131. Guischard, H. H.: Über das Wesen, die Notwendigkeit und Breite der Eisen- und Kupfertherapie, Med. Monatsschr. 3:364, 1949.

132. Hagberg, B.: The Iron-Binding Capacity of Serum in Infants and Children, Acta pædiat. (Supp. 93) 42:1, 1953.

133. Hahn, P. F.: The Use of Radioactive Isotopes in the Study of Iron and Hemoglobin Metabolism and the Physiology of the Erythrocyte, Advances Biol. & M. Physics 1:287, 1948.

134. Hahn, P. F., and Whipple, G. H.: Iron Metabolism: Its Absorption, Storage and Utilization in Experimental Anemia, Am. J. M. Sc. 191: 24, 1936.

135. Hahn, P. F.; Bale, W. F.; Lawrence, E. O., and Whipple, G. R.: Radioactive Iron and Its Metabolism in Anemia, J. Exper. Med. 69:739, 1939.

136. Hahn, P. F., et al.: Radioactive Iron and its Excretion in Urine, Bile, and Feces, J. Exper. Med. 70:443, 1939.

137. Hahn, P. F., et al.: Iron Metabolism in Human Pregnancy as Studied with the Radioactive Isotope Fe^{59}, Am. J. Obst. & Gynec. 61:477, 1951.

138. Hallen, L.: Iron and Epithelium, Acta med. scandinav., Supp. 90, p. 398, 1938.

139. Hamilton, L. D.; Gubler, C. J.; Cartwright, G. E., and Wintrobe, M. M.: Diurnal Variation in the Plasma Iron Level of Man, Proc. Soc. Exper. Biol. & Med. 75:65, 1950.

140. Hamilton, L. D., et al.: Studies on the Relationship of the Adrenal Cortex to the Experimental Production of Hypoferremia in Rats, Endocrinology 48:44, 1951.

141. Hedinger, C.: Zur Pathologie der Hämochromatose: Hämochromatose als Syndrom, Helvet. med. acta (Supp. 32) 20:1, 1953.

142. Heilmeyer, L.: Über die Pathogenese der echten Chlorose: Untersuchungen des Eisenstoffwechsels bei 2 Fällen von schwerer Chlorose, zugleich ein Beitrag zur Kenntnis der Eisenmangelerkrankungen, Deutsches Arch. klin. Med. 182:150, 1938.

143. Heilmeyer, L.: Pathologische Physiologie des Eisenstoffwechsels der Leber, Verhandl. deutsch. Gesellsch. Verdauungskr., 1954.

144. Heilmeyer, L.: Die Hämochromatose: Klinik, Eisenstoffwechsel und Pathogenese, Acta haemat. 11:137, 1954.

145. Heilmeyer, L.: Neuere Ergebnisse der Eisenstoffwechselforschung bei der Hämochromatose, Deutsche med. Wchnschr. 79:280, 1954.

146. Heilmeyer, L.: Ferritinstudien, Deutsche med. Wchnschr. 80:1377, 1955.

147. Heilmeyer, L., and Begemann, H.: Blut und Blutkrankheiten, in Handbuch der innern Medizin, edited by G. von Bergmann, W. Frey, and H. Schwiegk, Berlin, Springer-Verlag, 1951.

148. Heilmeyer, L.; Keiderling, W., and Stüwe, G.: Kupfer und Eisen als körpereigene Wirkstoffe und ihre Bedeutung beim Krankheitsgeschehen, Jena, VEB Gustav Fischer Verlag, 1941.

149. Heilmeyer, L., and von Mutius, I.: Untersuchungen über die Herauslösung von Eisen aus Nahrungsmitteln durch Magensaft und Galle: Zugleich ein Beitrag über den Gehalt der wichtigsten Nahrungsmittel an herauslösbarem Eisen, Ztschr. ges. Exper. Med. 112:192, 1943.

150. Heilmeyer, L., and Plötner, K.: Das Serumeisen und die Eisenmangelkrankheit (Pathogenese, Symptomatologie und Therapie), Jena, VEB Gustav Fischer, Verlag, 1937.

151. Hemmeler, G.: Serumeisen und Leber, Klin. Wchnschr. 18:1245, 1939.

152. Hemmeler, G.: L'Anémie infectieuse, Helvet. méd. acta 13:20, 1946.

153. Hemmeler, G.: Les Principes du traitement par le fer, Helvet. med. acta 13:488, 1946.

154. Hemmeler, G.: Mécanisme et régulation de la resorption du fer, Schweiz. med. Wchnschr. 80: 599, 1950.

155. Hemmeler, G.: Métabolisme du fer: Physiologie, pathologie, traitement, Paris, Masson & Cie, 1951.

156. Hemmeler, G.: Der Eisenstoffwechsel im Rahmen neurovegetativer Regulationen, Acta neuro-veg. 6:347, 1953.

157. Hendrych, F., and Weden, H.: Kobalt und Nickel, in Handbuch der Experimentellen Pharmakologie, edited by A. Heffter and W. Heubner, Berlin, Springer-Verlag, 1934, Vol. 3, p. 1401.

158. Hoet, J., and Lederer, J.: Données nouvelles sur les anémies et la thérapeutique martiale, Rev. méd. Louvain p. 134, 1939.

159. Hoet, J., and Renaer, M.: Le Fer sérique du nouveau-né, Acta biol. belg. 3:158, 1943.

160. Hoff, F.: Beiträge zur Frage der Blutregulation, Verhandl. deutsch. Gesellsch. inn. Med., Kong. 45, p. 124, 1933.

161. Holmberg, C. G., and Laurell, C. B.: Studies on the Capacity of Serum to Bind Iron, Acta physiol. scandinav. 10:307, 1945.

162. Holmberg, C. G., and Laurell, C. B.: Investigations in Serum Copper: I. Nature of Serum Copper and Its Relation to the Iron-Binding Protein in Human Plasma, Acta chem. scandinav. 1: 944, 1947.

163. Holmberg, C. G., and Laurell, C. B.: Investigations in Serum Copper: II. Isolation of the Copper Containing Protein and Description of some of its Properties, Acta chem. scandinav. 2:550, 1948.

164. Houssay, B. A.; Royer, M., and Orias, O.: Hémoglobine et nombre d'érythrocytes des chiens hypophysoprives, Compt. rend. Soc. biol. 108:496, 1931.

165. Høyer, K.: Serumjernets fysiologiske variation, Universitetsforlaget, Aarhus, 1946.

166. Hubble, D.: The Influence of the Endocrine System in Blood Disorders, Lancet 2:113, 1933.

167. Hume, D. M., and Wittenstein, G. J.: The Relationship of the Hypothalamus to Pituitary-Adrenocortical Function, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, New York, The Blakiston Company (division of McGraw-Hill Book Company, Inc.) 1950, p. 134.

168. Indovina, I.: Fisiopatologia del ferro e suoi rapporti con i bioregolatori, Catania, Agnini, 1948.

169. Indovina, I.: Distribution of Intravenously Injected Colloidal Radioactive Iron in Iron Proteins of Normal Rabbit and of Rabbits with Turpentine Abscess and Diphtheria Toxicosis, Am. J. Physiol. 165:348, 1951.

170. Indovina, I.; Savagnone, E., and Indovina, T.: Prime ricerche sulle modificazioni indotte dall'ACTH sulla sideremia in rapporto con tasso dell'acido urico, della creatinina e degli eosinofili del sangue, Boll. Soc. ital. biol. sper. 29:775, 1953.

171. Influence of Route of Administration and of Sex on Serum Iron Levels, Editorial, Nutrition Rev. 10:210, 1952.

172. Jasinski, B.: Eisenmangelzustände und ihre Therapie mit neuen Ferrosalzen, Helvet. med. acta 16:67, 1949.

173. Jasinski, B.: Über Pathogenese und Therapie der nichtanämischen und leicht-anämischen Eisenmangelzustände, Schweiz. med. Wchnschr. 79:1255, 1949.

174. Johnston, F. A.: New Developments in Theory of Iron Metabolism, J. Am. Dietet. A. 27:739, 1951.

175. Justin-Besançon, L.; Klotz, H. P., and Clement, D.: Les Anémies du panhypopituitarisme, presented at Congrès de Médecine Interne, Stockholm, 1954.

176. Justin-Besançon, L.; Klotz, H. P., and Clement, D.: Sur 2 Anémies d'origine hypophysaire: Leur Réparation par perfusions intraveineuses d'ACTH, Bull. et mém. Soc. méd hôp. Paris 70:70, 1954.

177. Kaldor, I.: Studies on Intermediary Iron Metabolism: 4. Haemoglobin Value, Serum Iron and Iron Binding Capacity in Normal and Castrated Rats, Australian J. Exper. Biol. & M. Sc. 32:437, 1954.

178. Kaldor, I.: Studies on Intermediary Iron Metabolism: 6. The Absorption and Storage of

Iron in Experimental Anaemia, Australian J. Exper. Biol. & M. Sc. 32:801, 1954.

179. Kalk, H.: Klinik der Hämochromatose, Verhandl. deutsche Gesellsch. Verdauungskr. 1954.

180. Kato, K.: Iron-Cobalt Treatment of Physiological and Nutritional Anemia in Infants, J. Pediat. 11:385, 1937.

181. Kinney, T. D.; Hegstedt, M. D., and Finch, C. A.: Influence of Diet on Iron Absorption: Pathology of Iron Excess, J. Exper. Med. 90:137, 1949.

182. Kleckner, M. S., et al.: Clinical Features, Pathology, and Therapy of Hemochromatosis, J. A. M. A. 157:1471, 1955.

183. Kleinberg, W.; Gordon, A. S., and Charipper, H. A.: Effect of Cobalt on Erythropoiesis in Anemic Rabbits, Proc. Soc. Exper. Biol. & Med. 42:119, 1939.

184. Kletzien, S. W.; Buchwald, K. W., and Hudson, L.: Mineral Metabolism—Copper and Iron, Proc. Soc. Exper. Biol. & Med. 30:645, 1933.

185. Klucharev, L. A.: Iron Metabolism in Blood Loss and Shock, Arkh. Pat. 18:36, 1956; abstracted Excerpta Med. II 10:480, 1957.

186. Kooyman, J. C.: De Ijzerstofwisseling, Utrecht, Academisch Proefschrift, 1947.

187. Kooyman, J. C.: Investigations on Serum- and Tissue-Iron, Acta med. scandinav. 134:205, 1949.

188. Korenchevsky, V., and Hall, K.: Effects of Sex Hormones on the Blood in Rats, J. Endocrinol. 4:103, 1945.

189. Kunde, M. M.; Green, M. F., and Burns, G.: Blood Changes in Experimental Hypo- and Hyperthyroidism, Am. J. Physiol. 99:469, 1932.

190. Lahey, M. E., et al.: Role of Copper in Erythropoiesis, Am. J. Physiol. 167:804, 1951.

191. Lahey, M. E., et al.: Studies on Copper Metabolism: III. Hematologic Manifestations of Copper Deficiency in Swine, Blood 7:1053, 1952.

192. Lambin, P., and Lederer, J.: Rapports des maladies du sang et des affections œso-gastro-duodénales: Aspects médicaux du problème, Acta gastro-enterol. belg. (Supp.) 14:315, 1951.

193. Lambrechts, A.; Dejardin, J., and Govaerts, J.: Allure de "résorption plasmatique" du chlorure ferreux et du gluconate ferreux administrés per os chez l'adulte normal, Acta biol. belg. 2:355, 1942.

194. Lambrechts, A., and Dejardin, J.: Fer plasmatique et glande thyroïde, Acta biol. belg. 3:248, 1943.

195. Lange, J., and Odenthal, H.: Zur Differenzialdiagnose und Verlaufsbeurteilung von Leber- und Gallenwegserkrankungen mit Hilfe der Serum-Eisen, -Kupfer und -Eiweissbestimmungen, Verhandl. deutsche Gesellsch Verdauungskr., 1954.

196. Larizza, P.: Ormoni sessauli ed emopoiesi, Haematologica 26:1, 1944.

197. Larizza, P., and Chirico, G.: Ricerche sperimentali sull'influenza della prolungata somministrazione di estratti paratiroidei sull'emopoiesi, Haematologica 36:653, 1952.

197. Larizza, P., and Chirico, G.: Azione degli estratti epifisari sul sangue periferico e sugli organi emolinfopoietici (ricerche sperimentali), Haematologica 37:101, 1953.

199. Larizza, P., and Chirico, G.: La posizione della tiroide nella regolazione dell'emopoiesi (ricerche sperimentali), Haematologica 38:771, 1954.

200. Larizza, P., and Notario, A.: Ipofisi ed emopoiesi (ricerche sperimentali), Haematologica 36:399, 1952.

201. Larizza, P.; Notario, A., and Ventura, S.: Estrogeni ed emopoiesi (ricerche cliniche e sperimentali), Haematologica 33:391, 1949.

202. Larizza, P.; Ventura, S., and Meduri, D.: Influenze ormoniche nella regolazione del ferro serico: Azione degli estratti epifisari, Haematologica 37:641, 1953.

203. Larizza, P.; Ventura, S.; Meduri, D., and Larizza, L.: Influenze ormoniche nella regolazione del ferro serico: Azione degli estratti ed ormoni ipofisari, Haematologica 38:611, 1954.

204. Larsen, V., and Lassen, N. A.: Serum Iron and Adrenocortical Function, with Special Regard to Stress Hypoferriemia, Acta med. scandinav. 154:65, 1956.

205. Lato, M.: Ricerche sulla sideremia: La sideremia in rapporto con l'alimentazione, Clin. pediat. 33:236, 1951.

206. Lato, M.: Ricerche sulla sideremia dei lattanti: La sideremia in rapporto con l'età del lattante, Clin. pediat. 33:425, 1951.

207. Laurell, C. B.: Studies on Transportation and Metabolism of Iron in the Body, with Special Reference to Iron-Binding Component in Human Plasma, Acta physiol. scandinav. (Supp. 46) 14:1, 1947.

208 Laurell, C. B.: What Is Function of Transferrin in Plasma? Blood 6:183, 1951.

209. Laurell, C. B.: The Diurnal Variation of the Serum Iron Concentration, Scandinav. J. Clin. & Lab. Invest. 5:218, 1953.

210. Lawrence, J. H.; Berlin, N. I., and Huff, R. L.: The Nature and Treatment of Polycythemia: Studies on 263 Patients, Medicine 32:323, 1953.

211. Lederer, J.: La Physiopathologie du fer, Louvain, Warny, 1940.

212. Lederer, J.: L'Asidérose, maladie par carence de fer, Scalpel 94:899, 1941.

213. Lederer, J.: Les Travaux belges sur la physiopathologie du fer dans l'organisme vivant, Arch. med. belg., Bruxelles 1:241, 1946.

214. Lederer, J.: Sur la Nature du fer sérique: Étude de la dialyse du fer sérique et du fer ajouté

au sérum, Arch. internat. pharmacodyn. 76:383, 1948.

215. Lederer, J.: Hyperthyroïdies partiellement masquées par une carence en fer, Ann. endocrinol. 10:603, 1949.

216. Lederer, J.: Rôle intermédiaire du fer dans l'elévation du metabolisme basal d'origine hyperthyroïdienne, Arch. internat. pharmacodyn. 81:382, 1950.

217. Lederer, J.: L'Anémie agastrique, Semaine hôp. Paris 27:1975, 1951.

218. Lederer, J., and Ferrin, J.: Trois Cas d'asidérose, J. belge gastro-entérol. 8:266, 1940.

219. Lederer, J., and Canivez, R.: Le Métabolisme du fer chez l'eunuque, Ann. endocrinol. 14: 653, 1953.

220. Lederer, J.; Canivez, R., and Prinzie, A.: Hormones sexuelles, métabolisme du fer et hémochromatose, Semaine hôp. Paris (Arch. biol.) 30: 12, 1954.

221. Lemaire, A.; Loeper, J., and Loeper, J.: Etude du fer sérique dans certaines affections hépatiques et endocriniennes, Presse méd. 57:1117, 1949.

222. Lerman, J., and Means, J. H.: Treatment of the Anemia of Myxoedema, Endocrinology 16: 533, 1932.

223. Librach, I. M.: Toxic Reactions Due to Intravenous Iron, Brit. M. J. 1:21, 1953.

224. Locke, A.; Main, E. R., and Rosbach, D. O.: The Copper and Non-Hemoglobinous Iron Contents of the Blood Serum in Disease, J. Clin. Invest. 11:527, 1932.

225. Losdyck, M., and Prinzie, A.: L'Intérêt diagnostique du taux de fer sérique dans les affections hépatiques, Acta gastroenterol. belg. 19:409, 1956.

226. Louis-Bar, D.: Endocrines et anémie, Rev. méd. Liége 4:293, 1949.

227. Lucia, S. P., and Marasse, H. F.: The Central Nervous System and Hematopoiesis, J. Nerv. & Ment. Dis. 99:734, 1944.

228. Lund, C. J.: Studies on the Iron Deficiency Anemia of Pregnancy, Including Plasma Volume, Total Hemoglobin, Erythrocyte Protoporphyrin in Treated and Untreated Normal and Anemic Patients, Am. J. Obst. & Gynec. 62:947, 1951.

229. Mallory, F. B.: Hemochromatosis and Chronic Poisoning with Copper, Arch. Int. Med. 37:336, 1926.

230. Mallory, F. B., and Parker, F., Jr.: Experimental Copper Poisoning, Am. J. Path. 7:351, 1931.

231. Mallory, F. B., and Parker, F., Jr.: The Microchemical Demonstration of Copper in Pigment Cirrhosis, Am. J. Path. 7:365, 1931.

232. Mandart, M., and Sonnet, J.: La Forme anémique de la hernie de l'hiatus œsophagien, Acta gastro-enterol. belg. 14:536, 1951.

233. Mansfeld, G.: Blutbildung und Schilddruse, Arch. Physiol. 152:23, 1913.

234. Mansfeld, G., and Sos, J.: Über die Beziehungen der Schilddrüse zur perniziösen Anämie, Klin. Wchnschr. 17:386, 1938.

235. Marie, P. L.: Métabolisme du fer du sérum, Presse méd. 165 and 196, 1944.

236. Marshall, F. H. A.: The Physiology of Reproduction, London, Longmans, Green & Co., Ltd., 1932.

237. Masshoff, W.: Eisenstoffwechsel und Leber, Verhandl. deutscher Gesellsch. Verdauungskr., 1954.

238. Matthes, M., and Kramer, G.: Der Eisenbedarf des Blutspenders, Deutsche med. Wchnschr. 81:1262, 1956.

239. Mayer, M., and Dreyfus, C.: Les Anémies de la grossesse, Semaine hôp. Paris 25:3925, 1949.

240. Mazur, A.; Litt, I., and Shorr, E.: Chemical Properties of Ferritin and Their Relation to Its Vasodepressor Activity, J. Biol. Chem. 187:473, 1950.

241. McCullagh, E. P., and Jones, R.: Effects of Androgens on the Blood Count of Men, J. Clin. Endocrinol. 2:243, 1942.

242. Meyer, O. O.; Thewlis, E. W., and Rusch, H. P.: The Hypophysis and Hemopoiesis, Endocrinology, 27:932, 1940.

243. Meythaler, F.: Über die hormonale Regulation des roten Blutbildes, Folia haemat. 69:299, 1950.

244. Michaud, L.: Il metabolismo del ferro, Rendic. Inst. super. san. 10:995, 1947.

245. Mies, H., and Richarz, G.: Zur Frage der vegetativen Steuerung des Serumeisenspiegels, Acta neuroveg. 5:165, 1952.

246. Moore, C. V.: Iron Metabolism and Hypochromic Anemia, in Symposia of Nutrition of the Robert Gould Research Foundation, 1947: Vol. I. Nutritional Anemias, p. 117, Cincinnati, The Robert Gould Research Foundation, Inc., 1947.

247. Moore, C. V.; Roberts, H., and Minnich, V.: A Study of the Selective Absorption of Iron with the Aid of its Radioactive Isotope, J. Clin. Invest. 20:436, 1941.

248. Mulder, B., and Noyons, E. C.: Over de ijzerbehoefte van het organisme, Nederl. tijdschr. geneesk. 91:3222, 1947.

249. Müller, F. Beiträge zur Frage nach der Wirkung des Eisens bei experimentell erzeugter Anämie, Arch. path. Anat. 164:436, 1901.

250. Muntwyler, E., and Hanzal, R. F.: Action of Copper and Other Elements in Iron Metabolism, Proc. Soc. Exper. Biol. & Med. 30:645, 1933.

251. Myhrman, G., and Wilander, O.: Inflammatory Anemia and Serum Iron Changes in Myocardial Infarction, Acta med. scandinav. 151:407, 1955.

252. Naegeli, O.: Blutkrankheiten und Blutdiagnostik: Lehrbuch der klinischen Hämatologie, Ed. 5, Berlin, Springer-Verlag, 1931.

253. Neale, F. C.: The Demonstration of the Iron-Binding Globulin (Transferrin) in Serum and Urine Proteins by Use of Fe^{59} Combined with Paper Electrophoresis, J. Clin. Path. 8:334, 1955.

254. Neukomm, S.: Contributon à l'étude des rapports entre le fer sérique et les protéines plasmatiques, Helvet. med. acta. 14:453, 1947.

255. Neukomm, S.: Contribution à l'étude du métabolisme du fer ionique, Schweiz. Zschr. Path. u. Bakt. 10:517, 1947.

256. Neukomm, S.: La Régulation physicochimique de la sidérémie, Acta haemat. 2:213, 1949.

257. Neuweiler, W.: Serumeisen in der Schwangerschaft und nach der Geburt, Ztschr. Geburtsh. u. Gynäk. 124:252, 1943.

258. Neuweiler, W.: Über die Eisenversorgung des Fötus, Schweiz. med. Wchnschr. 19:843, 1938.

259. Newcomer, J. S.: The Relation of the Hypophysis, Ovary, Placenta and Fetus to the Development of Anemia During the Last Half of Pregnancy in the Rat, Endocrinology 40:182, 1947.

260. Nicolle, P.: Recherches sur le rôle des hormones dans les variations physiologiques du taux réticulocytaire chez la lapine, compt. rend. Acad. sc. 203:1184, 1936.

261. Nordenson, N. G.: Clinical Experimental Observations on the Influence of Adreno-Corticotrophic Hormone (Corticotrophine) and Desoxycorticosterone (Doca) on the Peripheral Blood and the Bone Marrow, Acta med. scandinav. Supp. 196, p. 419, 1947.

262. Nordström, K.: The Reticulocyte Reaction in Hypoxia of Short Duration, Acta med. scandinav., (Supp. 326) 158:1, 1957.

263. Oebicke, B.: Wesen und Herkunft endogener Pigmente und ihre besondere Bedeutung für die Pigmentstoffwechselstörung der Hämochromatose, in Veröffentlichungen aus der morphologischen Pathologie, Heft 56, Band 12 (Schluss-) Heft 5, edited by W. Koch et al., Jena, Gustav Fischer Verlag, 1950.

264. Ossipovski, B.: Contribution à l'étude du métabolisme du fer: Le Métabolisme du fer au cours de la grossesse, Semaine hôp. Paris 27:2999, 1951.

265. Ossipovski, B.: Contribution à l'étude du métabolisme du fer, Thesis, Paris, 1951.

266. Ossipovski, B.: Le Fer en thérapeutique, Semaine hôp. Paris 31:802, 1955.

267. Overbeek, G. A.: The Influence of Thyroid and Pituitary on Iron Content of Blood Serum, Acta brev. neerland. 11:70, 1941.

268. Querido, A., and Overbeek, G. A.: Hypophysis and Blood Picture, Arch. internat. pharmacodyn. 59:370, 1938.

269. Overbeek, G. A., and Querido, A.: Hypophysis and Blood Picture, Arch. internat. pharmacodyn. 60:105, 1938.

270. Parella, M., and Rescigno, B.: Comportamento del ferro serico e suo valore nella tuberculosi pulmonare, Arch. tisiol. 9:198, 1954.

271. Patek, A. J., Jr., and Heath, C. W.: Chlorosis, J. A. M. A. 106:1463, 1936.

272. Piliero, S. J.; Landau, D., and Gordon, A. S.: The Adrenal Gland and Hemopoiesis, Science 112:559, 1950.

273. Pirart, J., and Carpent, G.: Aspects dynamiques de l'hémochromatose, Acta gastro-enterol. belg. 18:7, 1955.

274. Pommerenke, W. T.; Hahn, P. F.; Bale, W. F., and Balfour, W. M.: Transmission of Radioactive Iron to the Human Fetus, Am. J. Physiol. 137:164, 1942.

275. Powell, J. F.: Serum Iron in Health and Disease, Quart. J. Med. 13:19, 1944.

276. Present Knowledge of Iron and Copper in Human Nutrition, Editorial, Nutrition Rev. 4: 291, 1946.

277. Pribilla, W.: Das Verhalten des Ferri-Saccharates im Organismus und seine therapeutische Bedeutung, Arch. exper. Path. u. Pharmakol. 217:508, 1953.

278. Pribilla, W., and Gehrmann, G.: Untersuchungen über die Eisenversorgung des menschlichen Föten unter besonderer Berücksichtigung des Ferritins, Folia haemat., Frankfurt 1:23, 1956.

279. Prina, C.: Influenza della tiroide sulla sideremia ed assorbimento del ferro, Arch. sc. med. 91:478, 1951.

280. Prinzie, A.: Le Contrôle hormonal du fer sérique, Soc. Med. Chir. du Brabant, Bruxelles, Janvier, 1956.

281. Prinzie, A.: Effets des androgènes sur la sidérémie de la lapine traitée à la cortisone, Ann. endocrinol. 16:568, 1955.

282. Querido, A., and Overbeek, G. A.: Hypophysis and Bloodpicture, Arch. internat. pharmacodyn. 61:475, 1939.

283. Rath, C. E., et al.: Hematological Changes and Iron Metabolism of Normal Pregnancy, Surg. Gynec. & Obst. 90:320, 1950.

284. Rath, C. E., and Finch, C. A.: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation: XXXVIII. Serum Iron Transport; Measurement of Iron Binding Capacity of Serum in Man, J. Clin. Invest. 28:79, 1949.

285. Rechenberger, J.: Der Eisenstoffwechsel beim chronischen Infekt (Zugleich ein Beitrag zur Genese der Infektanämie), Deutsche Ztschr. Verdauungskr. 11:15, 1951.

286. Reimann, F.: Das Eisenmangelfieber: Ein Beitrag zur Kenntnis des inneren Krankheitsmechanismus bei den Eisenmangelanämien, sowie

zur Kenntnis der Fiebererscheinungen bei den Hunger- und Mangelzuständen, Acta haemat. 2: 247, 1949.

287. Reismann, K. R.; Boley, J.; Christiansen, J. F., and Delp, M. H.: The Serum Iron in Experimental Hepatocellular Necrosis, J. Lab. & Clin. Med. 43:572, 1954.

288. Remy, D.: Diskussion zum Thema "Eisenstoffwechsel und Leber," Verhandl. deutscher Gesellsch. Verdauungskr. 1954.

289. Remy, D.: Der Eisenstoffwechsel bei der Hämochromatose, Deutsche med. Wchnschr. 79: 1042, 1954.

290. Renaer, M.: Etude comparée de la résorption du chlorure ferreux à la fin de la grossesse et au cours des premiers jours du post-partum, Acta biol. belg. 2:36, 1942.

291. Renaer, M., Van Herendael, H. et Vandevelde, P.: La Résorption et la fixation du fer chez l'homme et chez la femme. C. R. Soc. Biol. 140: 591, 1946.

292. Robinson, J. C.; James, G. W., III, and Kark, R. M.: The Effect of Oral Therapy with Cobaltous Chloride on the Blood of Patients Suffering with Chronic Suppurative Infection, New England J. Med. 240:749, 1949.

293. Romberg, E. H.: Der Einfluss des vegetativen Nervensystems auf die Neubildung der Zellelemente des Blutes, Beihefte med. Monatsschr. 6:1, 1948.

294. Roth, F.: Beitrag zur Frage der antianämischen Wirkung des Kupfers, Med. Klin. 32: 1046, 1936.

295. Roth, O.: Eisenmangelerkrankungen bei Nicht-Anämischen, Schweiz. med. Wchnschr. 80: 1065, 1950.

296. Roth, O.; Jasinski, B., and von Bidder, H.: Das Gewebeeisen beim Menschen bei normalen und pathologischen Zuständen, Helvet. med. acta. 18:159, 1951.

297. Rothlin, E.: Beitrag zum Eisenstoffwechsel, Schweiz. med. Wchnschr. 74:583, 1944.

298. Rothlin, E.; Undritz, E., and Zehnder, K.: Contribution à l'étude du rôle du fer, du cuivre et du cobalt, Rev. path. gén. et physiol. clin. 56:1540, 1956.

299. Rovati, L.: Aspetti dell'anemia da latte nel ratto albino ed azione esercitata su di essa da alcuni composti di cobalto, Haematologica 38:441, 1954.

300. Ruhenstroth: Die Steuerung der Erythropoese, Deutsche med. Wchnschr. 79:1732, 1954.

301. Ruhenstroth-Bauer, G.: Versuche zum Nachweis eines spezifischen erythropoetischen Hormons, Arch. exper. Path. u. Pharmakol. 211:32, 1950.

302. Ruitinga, P., Jr.; Gaarenstroom, J. H., and Overbeek, G. A.: Hypophysis and Bloodpicture, Arch. internat. pharmacodyn. 64:109, 1940.

303. Rustung, E.: Studies of Serum Iron, Acta dermat.venereol. (Supp. 21) 29:1, 1949.

304. Sachs, A.; Levine, V. E., and Fabian, A. A.: Copper and Iron in Human Blood, Arch. Int. Med. 55:227, 1935.

305. Salera, U., and Tamburino, G.: Eisenaufnahme, Eisenreserve und Hämoglobinsynthese, Deutsche med. Wchnschr. 80:933, 1955.

306. Salter, W. T.: A Textbook of Pharmacology: Principles and Application of Pharmacology to the Practice of Medicine, Philadelphia, W. B. Saunders Company, 1952.

307. Schade, A. L., and Caroline, L.: An Iron-Binding Component in Human Blood Plasma, Science 104:340, 1946.

308. Schadt, E.: Eisenstoffwechselstudien, Inaugural Dissertation, Jena, 1940.

309. Schäfer, K. H.: Der Eisenstoffwechsel des wachsenden Organismus, Ergebn. inn. Med. u. Kinderh. 4:706, 1953.

310. Schäfer, K. H., and Boenecke, I.: Die neurovegetative Lenkung des Eisenstoffwechsels, Arch. exper. Path. u. Pharmakol. 207:666, 1949.

310. Schapira, G.: Le Fer radio-actif dans le diagnostic de laboratoire, Etudes de Biologie Clinique, 2e Série, Expansion Scientifique Française, Paris, 1953.

312. Schapira, G., and Dreyfus, J. C.: Métabolisme du fer, Exposés annuels biochim. méd. 15: 157, 1953.

313. Schiassi, F.: Il ferro inorganico nella cura delle anemie da menorragia e specialmente de metrorragie della pubertà: Importanza del ferro per la regolazione della funzione mestruale, Minerva med. 1:145, 1938.

314. Schiff, E.; Eliasberg, H., and Joffe, N.: Kupferbehandlung der Anämie im Säuglingsalter, Klin. Wchnschr. 9:2144, 1930.

315. Schlaphoff, D.; Johnston, F. A., and Boroughs, E. D.: Serum Iron Levels of Adolescent Girls and Diurnal Variation of Serum Iron and Hemoglobin, Arch. Biochem. 28:165, 1950.

316. Scholl, F., and Weinmann, O.: Eisenbelastung und Leberfunktion, Wien. med. Wchnschr. 101:991, 1951.

317. Scholten, R., and Veit, J.: Syncytiolyse und Hämolyse: Ein Beitrag zur Physiologie und Pathologie der Schwangerschaft, Ztschr. Geburtsh. u. Gynäk. 49:210, 1903.

318. Schrade, W.: Die Beeinflussung des Knochenmarks durch Sexualhormone, München. med. Wchnschr. 84:2005, 1937.

319. Schulhoff, K., and Matthies, M. M.: Polyglobulia Induced by Cerebral Lesions, J. A. M. A. 89:2093, 1927.

320. Schulten, H.: Physiologie und Pathologie des Eisenstoffwechsels, Deutsche med. Wchnschr. 78:117, 1953.

321. Schulze, M. O.: Some Biochemical Aspects of Metabolism of Iron and Copper, in Symposia on Nutrition of the Robert Gould Research Foundation, 1947: Vol. I., Nutritional Anemia, p. 99, Cincinnati, The Robert Gould Research Foundation, Inc., 1947.

322. Schunk, J., and Schmitt, G.: Tagesschwankungen der Magenazidität, Deutsche med. Wchnschr. 80:347, 1955.

323. Schwarzhoff, E.: Weitere Untersuchungen zur Frage der Beziehungen des Ovariums zur Blutbildung, Ztschr. ges. exper. Med. 99:214, 1936.

324. Schwarzhoff, E., and Vossschulte, K.: Über die Beeinflussung der Blutneubildung durch das Ovar beim Meerschweinchen und Kaninchen, Ztschr. ges. exper. Med. 107:419, 1940.

325. Schweitzer, C. H.: Eiweissmangel als ätiologisches Moment der Hämochromatose, Deutsche med. Wchnschr. 77:17, 1952.

326. Schwietzer, C. H.: Untersuchungen über das Hämosiderin, Acta haemat. 10:174, 1953.

327. Sharp, E. A., and Mack, H. C.: The Relationship of Hemopoietic Phenomena to Endocrine Disorders in Women, Endocrinology 24:202, 1939.

328. Sheldon, J. H.: Haemochromatosis, London, Oxford University Press, 1935.

329. Silvestroni, E., and Bianco, J.: Influenze del propionate di testosterone e della colesterina sull'ematosi (ricerche sperimentali nel ratto albino e sull'uomo), Policlinico (sez. med.) 48:381, 1941.

330. Skouge, E.:Klinische und experimentelle Untersuchungen über das Serumeisen, Inaugural Dissertation, Oslo, 1939.

331. Smith, N. J.: Symposium on Pediatrics: Iron Deficiency in Infants and Children, M. Clin. North America 36:1683, 1952.

332. Smith, S. E.; Medlicott, M., and Ellis, G. H.: The Blood Picture of Iron and Copper Deficiency Anemia in the Rabbit, Am. J. Physiol. 142:179, 1944.

333. Snapper, I.: Groen, J.; Hunter, D., and Witts, L. J.: Achlorhydria, Anaemia and Subacute Combined Degeneration in Pituitary and Gonadal Insufficiency, Quart. J. Med. 6:195, 1937.

334. Stander, H. J.: Williams Obstetrics: A Textbook for the Use of Students and Practitioners, Ed. 8, New York, Appleton-Century-Crofts, Inc., 1940.

335. Starkenstein, E.: Eisen, in Handbuch der experimentellen Pharmakologie, edited by A. Heffter and W. Heubner, Berlin, Springer-Verlag, 1934.

336. Stein, H. B., and Lewis, R. C.: The Stimulating Action of Copper on Erythropoiesis, J. Nutrition 6:465, 1933.

337. Steinglass, P.; Gordon, A. S., and Charipper, H. A.: Effect of Castration and Sex Hormones on Blood of the Rat, Proc. Soc. Exper, Biol. & Med. 48:169, 1941.

338. Stern, B., and Altschule, M.D.: Hematological Studies in Hypothyroidism Following Total Thyroidectomy, J. Clin. Invest. 15:633, 1936.

339. Stern, P.; Košak, R., and Misirlija, A.: Beitrag zur Frage der Eisenresorption, Experientia 10:227, 1954.

340. Stewart, G. E.; Greep, R. O., and Meyer, O. O.: Effect of Reduced Oxygen Tension upon Formed Elements of Blood of Hypophysectomized Animals, Proc. Soc. Exper. Biol. & Med. 33:112, 1935.

341. Stewart, W. B.: Some Aspects of the Metabolism of Iron, Bull. New York Acad. Med. 29:818, 1953.

342. Stich, W.: Zur Physiologie und Pathologie der eisenhaltigen Fermente der Leber, Verhandl. deutscher Gesellsch. Verdauungskr., 1954.

343. Stiefel, G. E., and Jasinski, B.: Le Fer colloïdal et son transport dans le sang, Semaine hôp. Paris (La Médecine dans le monde) 31:E83, 1955.

344. Stodtmeister, R.: Hypophyse und Blutbildung, Deutsche med. Wchnschr. 62:2010, 1936.

345. Stodtmeister, R., and Büchmann, P.: Moderne Eisentherapie, Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1943.

346. Stransky, E., and Vicente, C.: On Serum Iron Levels in Different Blood Diseases: Their Inportance for Differential Diagnosis, Ann. paediat. 180:163, 1953.

347. Sundelin, G.: Svenska läk.-tidning. 39:1451, 1942.

348. Sundstrom, E. S., and Michaels, G.: Mém. Univ. California 12:42, 1942.

349. Surgenor, D. M.: Koechlin, B. A., and Strong, L. E.: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation: XXXVII. The Metal-Combining Globulin of Human Plasma, J. Clin. Invest. 28:73, 1949.

350. Thaddea, S.: Über den Einfluss des Schilddrüsensenkretes auf die Blutbildung, Arch. exper. Pathol. u. Pharmakol. 166:276, 1932.

351. Thedering, F., Jr.: Zur vegetativen Steuerung des Serumeisens, Klin. Wchnschr. 27: 496, 1949.

352. Thedering, F., Jr.: Die kombinierte Kobalt-Eisen-Therapie bei Eisenmangelanämien, mit Einschluss des Eisenmangels beim Infekt und bei Tumoren, Med. Klin. 48:1144, 1953.

353. Thedering, F., and Gross, R.: Fortschritte mit der intravenösen Eisentherapie, Ztschr. ges. inn. Med. 4:634, 1949.

354. Thoenes, F., and Aschaffenburg, R.: Der Eisenstoffwechsel des wachsenden Organismus, S. Karger, Berlin, 1934.

355. Todt, H.: Klinische Eisenstoffwechseluntersuchungen, Inaugural Dissertation, Jena. 1939.

356. Tötterman, L. E.: Vitamin C and Iron Metabolism, Acta med. scandinav. (Supp. 230) 134:1, 1949.

357. Tyslowitz, R., and Hartmann, C. G.: Influence of Large Doses of Estrogens on the Blood Picture of Rhesus Monkeys (Macaca Mulatta), Endocrinology 29:349, 1941.

358. Vahlquist, B.: Das Serumeisen, Inaugural Dissertation, Uppsala, 1941.

359. Vahlquist, B.: Cause of Sexual Differences in Erythrocyte, Hemoglobin and Serum Iron Values in Human Adults, Blood 5:874, 1950.

360. Van Dyke, D. C., et al.: Maintenance of Circulating Red Cell Volume in Rats After Removal of Posterior and Intermediate Lobes of the Pituitary, Blood 7:1017, 1952.

361. Van Dyke, D. C.; Simpson, M. E.; Contopoulos, A. N., and Evans, H. M.: The Separate Existence of the Pituitary Erythropoietic Hormone, Blood 12:539, 1957.

362. Van Goidsenhoven, F.; Hoet, J., and Lederer, J.: Le Fer sérique en clinique humaine, Rev. belge sc. méd. 10:177, 1938.

363. Vannotti, A.: Anemie ipochromiche e metabolismo del ferro, Riv. clin. med. 49:233, 1949.

364. Vannotti, A., cited by Lederer, J.: Hyperthyroïdies partiellement masqués par une carence en fer, Ann endocrinol. 10:603, 1949.

365. Vannotti, A., and Delachaux, A.: Der Eisenstoffwechsel und seine klinische Bedeutung, Benno Schwabe, & Co., Basel, 1942.

366. Ventura, S: La transferrina, Haematologica 37:749, 1953.

367. Ventura S.: Il significato clinico della transferrina plasmatica, Haematologica 38:211, 425, and 587, 1954.

368. Ventura, S., and Gobbi, F.: La determinazione colorimetrica della transferrina: Influenza dell'emolisi, Haematologica 37:835, 1953.

369. Vollmer, E. P., and Gordon, A. S.: Effect of Sex and Gonadotropic Hormones upon the Blood Picture of Rats, Endocrinology 29:828, 1941.

370. Vollmer, E. P.; Gordon, A. S., and Charipper, H. A.: Effects of Hormones on Erythropoiesis in Hypophysectomized Rats, Endocrinology 31:619, 1942.

371. Vollmer, E. P.; Gordon, A. S.; Levenstein, I., and Charipper, H. A.: Effects of Hypophysectomy on the Blood Picture of the Rat, Endocrinology 25:970, 1939.

372. Vuilleumier, P.: Über die parenterale Eisentherapie der Anämien, Schweiz. med. Wchnschr. 76:50, 1946.

373. Waldenström, J., and Hallen, L.: Iron and Epithelium: Some Clinical Observations, Acta med. scandinav., Supp. 90, p. 380, 1938.

374. Waldenström, J.: Serum-Eisen und Eisenmangel bei der perniziösen Anämie, Schweiz. med. Wchnschr. 74:978, 1944.

375. Wallbach, G.: Gesetzmässigkeiten der vitalen Eisenspeicherung in den Zellen des tierischen Organismus, Protoplasma 29:122, 1937.

376. Wallenius, G.: A Note on Serum Iron Transportation, Scandinav. J. Clin. & Lab. Invest. 4:24, 1952.

377. Waltner, K., and Waltner, K.: Kobalt und Blut, Klin. Wchnschr. 8:313, 1929.

378. Warburg, O., and Krebs, H. A.: Über locker gebundenes Kupfer und Eisen im Blutserum, Biochem. Ztschr. 190:143, 1927.

379. Wasserman, L. R., and Loevinger, R.: Use of Radioactive Isotopes in Medicine, Advances Int. Med. 4:77, 1950.

380. Watkinson, G.: Hypopituitarism, Hypogonadism and Anemia. Lancet, 1947, 631.

381. Weissbecker, L.: Kobalt als Spurenelement and Pharmakon, Beihefte med. Monatsschr. 9:1, 1950.

382. White, A., and Dougherty, T. F.: Effect of Prolonged Stimulation of the Adrenal Cortex and of Adrenalectomy on the Number of Circulating Erythrocytes and Lymphocytes, Endocrinology 36:16, 1945.

383. Widdowson, E. M., and McCance, R. A.: Sexual Difference in Storage and Metabolism of Iron, Biochem. J. 42:577, 1948.

384. Wintrobe, M. M.: Physiological Implications of the Anemic State, in Symposia on Nutrition of the Robert Gould Foundation, 1947: Vol. I. Nutritional Anemia, p. 4, Cincinnati, The Robert Gould Research Foundation, Inc., 1947.

385. Wintrobe, M. M.: Clinical Hematology, Ed. 3, Philadelphia, Lea & Febiger, 1951.

386. Cartwright, G. E., et al.: The Anemia of Infection: I. Hypoferremia, Hypercupremia and Alterations in Porphyrin Metabolism in Patients, J. Clin. Invest. 25:65, 1946.

387. Cartwright, G. E., et al.: The Anemia of Infection: II. The Experimental Production of Hypoferremia and Anemia in Dogs, J. Clin. Invest. 25:81, 1946.

388. Wintrobe, M. M., et al.: The Anemia of Infection: III. The Uptake of Radioactive Iron in Iron-Deficient and in Pyridoxin-Deficient Pigs Before and After Acute Inflammation, J. Clin. Invest. 26:103, 1947.

389. Greenberg, G. R.; Ashenbrucker, H.; Lauritsen, M., and Wintrobe, M. M.: The Anemia of Infection: IV. The Lack of Relationship Between the Diversion of Iron from the Plasma and the Origin of the Anemia, J. Clin. Invest. 26:114, 1947.

390. Greenberg, G. R., et al.: The Anemia of Infection: V. Fate of Injected Radioactive Iron in the Presence of Inflammation, J. Clin. Invest. 26:121, 1947.

391. Wintrobe, M. M., et al.: The Anemia of Infection: VI. The Influence of Cobalt on the

Anemia Associated with Inflammation, Blood *2*: 323, 1947.

392. Cartwright, G. E., and Wintrobe, M. M.: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation: XXXIX. The Anemia of Infection; Studies on the Iron-Binding Capacity of Serum, J. Clin. Invest. 28:86, 1949.

393. Gubler, C. J.; Cartwright, G. E., and Wintrobe, M. M.: The Anemia of Infection: X. The Effect of Infection on the Absorption and Storage of Iron by the Rat, J. Biol. Chem. 184: 563, 1950.

394. Gubler, C. J.; Cartwright, G. E., and Wintrobe, M. M.: The Anemia of Infection: XI. The Effect of Turpentine and Cobalt on the Absorption of Iron by the Rat, J. Biol. Chem. 184: 575, 1950.

394. Cartwright, G. E.; Gubler, C. J., and Wintrobe, M. M.: The Anemia of Infection: XII. The Effect of Turpentine and Colloidal Thorium Dioxide on the Plasma Iron and Plasma Copper of Dogs, J. Biol. Chem. 184:579, 1950.

396. Cartwright, G. E., et al.: The Anemia of Infection: XIII. Studies on Experimentally Produced Acute Hypoferremia in Dogs and the Relationship of the Adrenal Cortex to Hypoferremia, J. Clin. Invest. 30:161, 1951.

397. Cartwright, G. E., and Wintrobe, M. M.: The Anemia of Infection: XVII. A Review, Advances Int. Med. 5:165, 1952.

398. Wintrobe, M. M., et al.: Effect of Corticotrophin and Cortisone on the Blood in Various Disorders in Man, A. M. A. Arch. Int. Med. 88: 310, 1951.

399. Wishinsky, H., et al.: Ethylenediaminetetraacetic Acid in the Mobilization and Removal of Iron in a Case of Hemochromatosis, J. Lab. & Clin. Med. 42:550, 1953; Correction 43:168, 1954.

400. Wöhler, F.: Zur Physiologie und Pathologie des Speichereisens: III. Über den intermediären Eisenstoffwechsel der Plazenta, Deutsche med. Wchnschr. 80:30, 1955.

401. Wright, C. S.; Mabry, D. S.; Carr, R. D., and Perry, A. M.: Survey of the 1953 Hematology Literature, A. M. A. Arch. Int. Med. 94:648, 1954.

402. Wuhrmann, F., and Jasinski, B.: Untersuchungen über die Bindung des Eisens an das Serumglobulin β, mit Hilfe des Radioeisens 59Fe und dessen klinische Bedeutung, Schweiz. med. Wchnschr. 83:661, 1953.

403. Yuile, C. L., et al.: Plasma and Red Cell Radioiron Following Intravenous Injection: Turpentine Abscesses in Normal and Anemic Dogs, J. Exper. Med. 90:273, 1949.

404. Zegla, P. S.: American Literature on Hematology of 1949: Review, Acta haemat. 4:232 and 306, 1950.

Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. Archives of Internal Medicine, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

A Bibliography of Internal Medicine

Auricular Fibrillation

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The story of the development of knowledge of auricular fibrillation, one of the most frequent and important of the cardiac arrhythmias, can be traced in interesting fashion through the various editions of Sir Thomas Lewis' great treatise (The Mechanism of the Heart Beat, London, Shaw and Sons, 1911; The Mechanism and Graphic Registration of the Heart Beat, London, Shaw and Sons, 1920, and Ed. 3, 1925). The older German point of view is set forth in Wenckebach's monograph (Die unregelmässige Herztätigkeit und ihre klinische Bedeutung, Leipsic, Wilhelm Engelmann, 1914) and the subject up to 1924 is thoroughly reviewed by W. E. Garrey (Auricular Fibrillation, Physiol. Rev. 4:215, 1924). An authoritative modern discussion is to be found in P. D. White's textbook (Heart Disease, New York, The Macmillan Company, Ed. 4, 1951). All these monographs contain comprehensive bibliographies.

Auricular Fibrillation

Circus movement in
  Reference 12
Clinical
  References 1, 5, 8, 10, 12
Effect of digitalis in
  References 8, 9
Electrocardiogram
  Reference 7
Experimental fibrillation
  Reference 6
General
  Reference 1
Inspection of auricles in
  Reference 13
Pathology
  Reference 3
Physiology
  References 2, 4, 5, 7, 12, 14, 15
Quinidine in
  Reference 11

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1. **Adams, R.** Cases of Diseases of the Heart Accompanied with Pathological Observations, Dublin Hosp. Rep. 4:353, 1827.

Adams was one of the first to describe clearly the clinical features of auricular fibrillation and definitely to relate it to mitral stenosis. "The more decided symptoms of this affection are to be found in the peculiar irregularity and want of correspondence in the pulse, as felt at the wrist and examined simultaneously at the heart; the latter often beats so violently against the sides of the thorax as to shake the patient in his bed, while at the same time the arterial pulse is small, weak, and irregular, . . . this irregularity, etc. . . . are not the only circumstances worthy of our attention, but the

pathognomonic sign will be found in this, that the heart will sometimes give two, three, or even four beats in succession, which are not perceptible to the hand examining the pulse in the arteries." And in another case: "I found . . . the action of the heart was rapid, strong and irregular, while the pulse at the wrist was weak and thready, and although its beat was for the most part synchronous with that of the heart there were often two, three or even four pulsations of the heart at a moment when all pulsation was suspended in the arteries and could not be felt by the finger placed accurately over the radial artery: the pulse counted here ranged at the rate of about 120 per minute and the beat of the heart, during the same time, exceeded by ten, twelve or fifteen, that number. I have never seen the pulsations in the jugular veins more evident than in this case, and I ascertained that their beats corresponded accurately with every pulse of the heart, even with those which were not felt in the arteries. . . . Having seen such an exact combination of symptoms as this in many cases which terminated fatally, and ascertained by an examination after death that their source was to be found in the narrowing of the aperture between the left auricle and ventricle, I have little doubt as to the nature of the cases." Thus Adams anticipated by 75 years the "ventricular pulse" of Mackenzie (Ref. 4) and also clearly recognized the association of totally irregular heart action with mitral stenosis. Others, even much later, were less precise and for the most part associated palpitation and rapid irregular pulse with nervousness.

Bertin (Bertin, R. J.: Traité des maladies du coeur et des gros vaisseaux, Paris, J. B. Baillière, 1824), a member of the great French school of clinician pathologists, stresses the anatomical changes. However, he says of valvular lesions that "the pulse, small, hard, unequal, irregular, intermittent, contrasts in its lack of force with the beating, often very energetic, of the heart; it is less irregular when the disease affects the valves of the right side than when it affects the left [p. 228]."

Hope (Hope, J.: A Treatise on the Diseases of the Heart and Great Vessels, London, William Kidd, 1832), in his important treatise, lists irregularities of the pulse under the general heading of "palpitation, particularly nervous," but in the section on mitral diseases he says "The pulse . . . may in valvular disease be small, weak, intermittent, irregular, and unequal, . . . the character of the pulse just described is most marked in contraction of the mitral valve: and if its contraction be great, they are all invariably present; for, as in this case, if the left ventricle is not freely supplied with blood it is not stimulated to contract to the natural intervals with suitable energy [p. 331]."

In Stokes' treatise (Stokes, W.: The Diseases of the Heart and the Aorta, Dublin, Hodges and Smith, 1854) there is no organized discussion of the arrhythmias. However, with reference to mitral disease, Stokes says "And with respect to irregularity, experience shows that this condition is more intimately connected with lesions of the muscles than of the valves of the heart [p. 175]." In this respect he differed from most contemporary observers.

Flint, the great American clinician, also is noncommittal (Flint, A.: A Practical Treatise on the Diagnosis, Pathology and Treatment of Diseases of the Heart, Philadelphia, Blanchard and Lea, 1859). "Weakness, smallness and irregularity, as well as intermittency and even irregularity, it is to be born in mind, are not distinctive of mitral or other valvular lesions. All these characters of the pulse may occur in cases of enlargement or fatty degeneration uncomplicated with lesions of the valves or orifices. All may occur, moreover, in merely functional disorders of the heart [p. 137]."

Fifteen years later Walshe (Walshe, W. H.: A Practical Treatise on the Diseases of the Heart and Great Vessels, London, Smith, Elder and Co., 1873) adds little. "A heart beating, now fifty, now one hundred

and eighty or more times a minute, now with excessive force, the next moment with such feebleness that the hand scarcely catches the impulse, cannot fail to become more or less clogged and obstructed internally [p. 179]." Walshe makes an advance in trying to explain the disturbances in terms of physiology, but the time was not yet ripe for a valid correlation. "The sphygmogram of the radial pulse translated all this in variations of verticalness of the line of ascent in different waves, in polycrotism of the line of descent varied with dicrotism etc., etc. [p. 179]."

Balfour (Balfour, G. W.: Clinical Lectures on Diseases of the Heart and Aorta, London, J. A. Churchill, Ltd., 1882) concurs with the earlier opinions. "I have already mentioned to you that extremely irregular action is almost pathognomonic of mitral stenosis [p. 256]," and on p. 137 there is a tracing of the radial pulse which undoubtedly indicates fibrillating auricles. Most arrhythmias, however, he, like the others, regards as "neurotic" or "hysterical."

Finally, in Osler's first edition (Osler, W.: The Principles and Practice of Medicine, New York, D. Appleton and Company, 1892) there is little on the question. Under mitral stenosis all we find is the following sentence: "Failure of compensation brings in its train the group of symptoms which have been discussed under mitral insufficiency: rapid irregular action of the heart . . . [p. 618]." But for the most part disturbances in rate and rhythm are dealt with under the heading of "Neuroses of the Heart." In a purely descriptive list one finds "(5) Delirium cordis, in which . . . the heart's action is wholly irregular [p. 651]." These statements remain unchanged in the second (1893), fourth (1901), and fifth (1903 editions. In the sixth (1905) edition, however, Osler has acquired some acquaintance with the work of Mackenzie, Wenckebach, and others, and so partial and complete heart block are mentioned. However, delirium cordis is now stated to be the result of irregularly recurring extrasystoles. This statement is preserved in the seventh edition (1909), and it is not until the eighth edition, in 1912, that the term "Fibrillation of the heart (Cardiac flutter, Nodal rhythm, Pulsus irregularis perpetuus)" appears.

All this illustrates very well the lag between scientific advance and general recognition in the textbooks.

2. **Marey, E. J.** Physiologie médicale de la circulation du sang, Paris, Adrien Delahaye, 1863.

"It has seemed to us that a systematic application of physiology to medicine is possible today, thanks to the labors of modern physiologists, and we have tried, with reference to one function, the circulation of the blood, to show what light physiological notions can throw on the phenomena of disease." This, the opening paragraph of Marey's book, written in 1863, shows how the clinicians (Ref. 1) failed to note or to learn for the next 50 years the important discoveries made with the sphygmomanometer. Marey's monumental volume of nearly 600 pages, filled with beautiful tracings, beginning with one which shows clearly the time relations of auricular and ventricular beating, touches on every aspect of the circulation in health and in disease. He recognizes the tendency to totally irregular pulse in mitral disease and presents a tracing (Fig. 200, p. 525) which is obviously that of auricular fibrillation. In Germany, too, at about this time a tremendous amount of work was done with the sphygmomanometer, but again, while pulse tracings obviously from cases of auricular fibrillation were shown, the writers had not the slightest idea what sort of disturbance of mechanism existed (Sommerbrodt, J.: Über Allorhythmie und Arhythmie des Herzens und deren Ursachen, Deutsches Arch. klin. Med. 19: 392, 1877), and while F. Riegel (Über den normalen und pathologischen Venenpuls, Deutsches Arch. klin. Med. 31:1, 1882) presented beautiful curves of the venous pulsations in the neck in addition to arterial pulse curves, his article contains no report of anything resembling auricular fibrillation.

3. **Radasewsky, M.** Über die Muskelerkrankungen der Vorhöfe des Herzens, Ztschr. klin. Med. 27:381, 1895.

As doctors did later with Cushney's observations (Ref. 6), so too they overlooked the hints which might have been gleaned from Radasewsky's anatomical work. Radasewsky made a careful correlation between the clinical condition and the histology of the auricles at autopsy. He concludes, "the marked irregularity of the heart often observed in the presence of chronic myocarditis may be caused by disease of the auricles and not by changes in the ventricles."

4. **Mackenzie, J.** The Study of the Pulse, Arterial, Venous, and Hepatic and of the Movements of the Heart, Edinburgh and London, Young J. Pentland, 1902.

Mackenzie, that indefatigable exponent of the sphygmograph, in this important book first related paralysis of the auricles to the ventricular form of venous pulse. However, he speaks of a gradual waning of the auricular pulse waves during cardiac failure and a gradual return during improvement. Also, interestingly enough, he does not mention mitral disease especially or irregularity at all.* He had at this time, therefore, the simple concept that greatly dilated auricles might become "paralyzed" at any time, regardless of rate or rhythm of the heart, with return to normal auricular beating at any time that dilation was lessened. But a few years later Mackenzie (The Inception of the Rhythm of the Heart by the Ventricle, Brit. M. J. 1:529, 1904) states positively with reference to cases with totally irregular rapid pulse: "As a result of a study of a large number of cases where a jugular pulse was present I have been able to establish the fact that the cause of the irregularity is due to the rhythm of the heart proceeding from the ventricles, and not, as normally, from the great veins as they debouch into the auricles." Not only this but where there was no auricular wave Mackenzie inferred that in certain cases the auricle and ventricle were beating simultaneously. He supports his thesis by argument from numerous arterial and venous tracings and not at this time by autopsy findings of hypertrophied auricles, which later made him believe that the auricles could not be paralyzed. Mackenzie shows his keen clinical sense, however, when from observation of the onset of fibrillation he says, "These symptoms which follow definitely the beginning of an attack of continuous irregularity are those we meet with in advanced cases, and it is for that reason I suggest that it is the irregularity that is the cause of the inefficient heart action and not the dilatation that causes the irregularity." Still later Mackenzie (The Interpretation of the Pulsations in the Jugular Veins, Am. J. M. Sc. 134:12, 1907) states, "One conclusion I have come to, and it is this, that when the ventricular venous pulse is present the heart's contraction proceeds no longer from the normal place . . . but probably from the fibers joining auricle and ventricle."

Finally Mackenzie (Abnormal Inception of the Cardiac Rhythm, Quart. J. Med. 1: 39, 1907-1908) formulated his views on the disturbed mechanism of totally irregular pulse. "The proposition I wish to present is that in these cases the normal sequence of the heart's contraction no longer prevails, that the ventricles alone may contract, or that the auricles and ventricles contract simultaneously. . . . I suggest that the stimulus for contraction arises no longer from the normal place . . . e. g. from the sinus node . . . but at the a-v node (Knoten) described by Aschoff and Tawara situated at the auriculo-ventricular junction." The argument was that all evidence (sphygmographic) of activity of the auricle was absent; it was therefore presumably paralyzed. In some cases the auricles observed at autopsy were hypertrophied and there-

* I have searched in vain for verification of Sir Thomas Lewis' statement (The Mechanism of the Heart Beat, London, Shaw and Sons, 1911): "In the work referred to this writer first demonstrated their frequent association [gross irregularity and the ventricular venous pulse] and ascribed them both to a single underlying condition, namely paralysis of the auricle [p. 195]."

fore could not be paralyzed. Simultaneous beating of auricle and ventricle with impulse arising in the A-V node (nodal rhythm), Mackenzie therefore thought, must be the explanation, the auricular beat being concealed by the ventricular contraction in the sphygmogram. All this was the reasoning of a keen but stubborn physician equipped with inadequate methods, since the mechanism of auricular fibrillation was promptly elucidated by the electrocardiograph. Mackenzie, however, was aware by this time that totally irregular pulse could occur not only with mitral disease but in the elderly with senile or arteriosclerotic changes.

5. **Hering, H. E.** Analyse des Pulsus irregularis perpetuus, Prag. med. Wchnschr. 38:377, 1903.

While Mackenzie's opinions (Ref. 4) held the spotlight in English-speaking countries, a mass of work was being done in Germany and France on the cardiac irregularities. Hering first concluded that the totally irregular pulse which persisted for an indefinite period was a specific arrhythmia to be distinguished from all others. He named it pulsus irregularis perpetuus. He felt that this disturbance not only was long lasting but was the same whether the heart beat fast or slow; that it was not affected by breathing; that it occurred with valve lesions, coronary sclerosis, and myocardial disease, and that therefore it was of cardiac and not of neurogenic origin. Hering later analyzed the problem at length (Über den Pulsus irregularis perpetuus, Deutsches Arch. klin. Med. 94:185, 1908), but it was becoming obvious that no further knowledge was to be gained from sphygmomanometry alone. It was only later that transient auricular fibrillation was first recognized (Ref. 10).

6. **Cushny, A. R., and Edmunds, C. W.** Paroxysmal Irregularity of the Heart and Auricular Fibrillation, Am. J. M. Sc. 133: 66, 1907.

Cushny, the pharmacologist, had for years, in cooperation with George Dock, been studying the physiology of irregularities of the pulse. In an early paper (Cushny, A. R.: On the Interpretation of Pulse Tracings, J. Exper. Med. 4:327, 1899) he says: "A few words may be added in regard to the extreme irregularity of the heart known clinically as delirium cordis. . . . The clinical sphygmogram in these cases resembles exactly that obtained from dogs when the auricle is undergoing fibrillary contractions, which may be continued for a long time without proving fatal. I do not wish to assert that the clinical delirium cordis is identical with the physiological delirium auriculae, but the resemblance is certainly striking. The fibrillary contraction of the auricle may be induced by stimulating it by means of rapid induction shocks and possibly by other forms of stimulation." But in spite of this hint clinicians seemed to pay no attention to the possibility of auricular fibrillation being the explanation of the rapid totally irregular pulse of patients.† In a paper eight years later, Cushny was still hammering away. He observed a patient with paroxysms of total irregularity and analyzed the arterial pulse tracings. Apropos of Mackenzie's views on nodal rhythm, Cushny says "In our tracings then, there is nothing to suggest that the ventricle originated the rhythm anywhere . . . [the ventricle] seems rather to have merely responded to the impulses which it received at irregular intervals from the auricle. Not infrequently the impulses followed each other so rapidly that the ventricle could not dilate sufficiently in the interval to permit the entrance of blood from the auricle." Cushny again compares this rhythm with auricular fibrillation in dogs produced in the laboratory by induction shocks, overdosage with digitalis, and other means. "The suggestion is made that in the patient described and in other cases of paroxysmal arrhythmia the condition is due to auricular fibrillation from inhibition of the vagus centre." But American and English students

† The actual clinical case history of Cushny's patient is given by M. Block (The Earliest Correlation of Clinical and Experimental Auricular Fibrillation, Am. Heart J. 18:684, 1939).

were so dominated by Mackenzie's views that it was not until this second paper appeared that they began to consider the possibility of auricular fibrillation being the cause of irregular rapid pulse.

7. **Hering, H. E.** Das Elektrocardiogramm des Irregularis perpetuus, Deutsches Arch. klin. Med. 94:205, 1908.

Hering seems to have been the first, in this brief article, to report on electrocardiograms of patients with totally irregular pulse.‡ He studied two cases. "It turned out that one could see in the electrocardiogram no signs of action of the supraventricular division of the heart, that is to say of the auricles." ECG's are reproduced, showing absence of regularly spaced P waves preceding R waves and with F waves. The full interpretation of the tracings was, however, not clear to Hering. In a later article (Über das Fehlen der Vorhofzacke (P) im Electrocardiogramm beim Irregularis perpetuus, München. med. Wchnschr. 56: 2483, 1909) he reviews the work of others. C. J. Rothberger and H. Winterberg (Vorhofflimmern und Arrhythmia perpetua, Wien. klin. Wchnschr. 22:839, 1909), remembering Cushny's suggestion (Ref. 6), thought, on the basis of resemblance of the disturbance in dogs and in man, that the electrocardiographic tracings from cases of totally irregular pulse indicated that fibrillation of the auricles (Vorhofflimmern) was present. With this view Hering did not agree, since he believed that fibrillation was incompatible with the long duration of the disturbance usually observed in man. Although T. Lewis had been working on the subject, his first mention of the electrocardiogram came in a brief note (Auricular Fibrillation: A Common Clinical Condition, Brit. M. J. 2:1528, 1909) following the German publications. In this note, however, he summarizes all the important features, clinical and electrocardiographic, of the disorder and leaves no doubt that it is due to auricular fibrillation. "It provides us with a rational understanding of the disorderly nature of the ventricular rhythm for it is dependent upon the irregular auricular movements," a statement shown later to be not quite accurate. "It explains the slowing which is obtained by digitalis" by increasing block in the conduction system.

8. **Lewis, T.** Auricular Fibrillation and Its Relationship to Clinical Irregularity of the Heart, Heart 1:306, 1909-1910.

This article, or rather brief monograph, is a brilliant exposition in Sir Thomas Lewis' best style of all that was known, clinically and in the laboratory, on auricular fibrillation. Only a few points of importance were subsequently added. The article opens with a historical survey of development of knowledge. Next comes a clinical analysis of 73 cases. After a section on the sphygmomanometric tracings the electrocardiograms are described in detail. "Complete irregularity of the heart is the result of auricular fibrillation. The irregular oscillations seen upon galvanometric curves are due to an incoordinate contraction of some portion of the heart. . . . The irregular oscillations arise in the vicinity of the auricle. The constancy of the oscillations, their unique appearance and their presence throughout the whole of the cardiac cycle is responsible for the conviction that they are an essential feature of complete irregularity and that the activity of the auricle is continual . . . coordinate contraction of the auricle is absent . . . oscillations similar to those characterizing complete irregularity of the heart in man are found experimentally when the auricle is fibrillating, and the oscillations are produced in the auricle as a result of fibrillation." Lewis was very clear as to the action of digitalis in auricular fibrillation: "Digitalis retards the ventricular rate in clinical auricular fibrillation by enhancing a previously existing auriculoventricular heart-block. The rapid and

‡ In the classical paper by W. Einthoven (Le Telecardiogramme, Arch. Internat. de Physiol. 4: 132, 1906-1907) on the clinical use of the electrocardiograph there is reproduced a tracing showing auricular fibrillation (Fig. 31), but Einthoven does not relate this to any specific disturbance or to a totally irregular pulse.

irregular impulses showered upon the ventricle from the fibrillating auricle are hindered in their passage from one chamber to the other by the action of drugs of this class. The influence of digitalis is exerted, directly or through the vagus, upon the junctional tissues." Lewis, later, in terms of the circus movement theory of fibrillation carefully analyzed the action of digitalis (The Action of Digitalis in Cases of Auricular Fibrillation, Am. J. M. Sc. 164: 157, 1922).

9. **Lewis, T.** The Reaction of the Heart to Digitalis When the Auricle Is Fibrillating, Brit. M. J. 2:1670, 1910.

Lewis gives J. Mackenzie credit for first demonstrating the potency of digitalis in slowing the ventricular rate in auricular fibrillation (Mackenzie, J.: IV. Action of Digitalis on the Human Heart in Cases Where the Inception of the Rhythm of the Heart is Due to the Ventricle, Brit. M. J. 1: 759, 1905). Mackenzie, however, who still believed that the mechanism in fibrillation was that of "nodal rhythm" (Ref. 4), although he shows sphygmographic tracings from a patient demonstrating the slowing, was completely confused as to the mode of action. "The effect . . . is mainly, if not entirely, an effect on the contractility." Mackenzie apparently had no idea of the concept of block in the conduction system.

Lewis, therefore, seems to give the first definitive account of the action of digitalis in auricular fibrillation. "Thus, while each contraction of the ventricle is of a similar nature to a normal systole, the sequence of contraction presents no rhythm but has a completely disordered character. In explanation of this gross irregularity in the ventricle it is supposed that occasional impulses escape in a haphazard fashion from the turmoil in the auricle, and that, like normal impulses they are transmitted across the junctional tissues . . . to the ventricle. . . . The case for which I plead [is] that digitalis slowing is the result of heart block when the auricle is fibrillating." However, Lewis postulated the presence of a partial heart block to begin with and apparently did not recognize at that time that the normal refractory period of the ventricle prevented it from responding to all of the many impulses from the auricle which were bombarding it in auricular fibrillation. Nonetheless, he emphasized the concept correctly as a whole. Digitalis dosage was not yet understood, however, and was usually too small. In the case pictured by Mackenzie, for example, several years later, six days elapsed before slowing of the ventricle even began. The patient was from the start given small doses of digitalis tincture—15 minims (1.0 cc.) four times daily (Mackenzie, J.: The Schorstein Lectures on Auricular Fibrillation, Brit. M. J. 1:869, 1911).

10. **Gossage, A. M., and Hicks, J. A. B.** On Auricular Fibrillation, Quart. J. Med. 6: 435, 1913.

Auricular fibrillation was traditionally regarded as a permanent disturbance (pulsus perpetuus irregularis) dependent on disease of the myocardium (Ref. 3, 5). But Gossage and Hicks reported cases in which the disturbance arose suddenly where there had been no previous sign or symptom of heart disease. They raised the possibility that it occurs in hearts previously perfectly healthy. In one patient who died suddenly histological study showed no disease of the heart. Numerous reports on auricular fibrillation in otherwise normal hearts have appeared since the paper of Gossage and Hicks. I. C. Brill (Auricular Fibrillation: The Present Status with a Review of the Literature, Ann. Int. Med. 10:1487, 1937) reviews the literature to 1937, and later E. Phillips and S. A. Levine report 84 instances of fibrillation in apparently normal hearts (Auricular Fibrillation Without Other Evidence of Heart Disease, Am. J. Med. 7:478, 1949). Of these, 61 had permanent fibrillation, whereas in 23 the disturbance was paroxysmal or transient.

11. Frey, W. Über Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin, Berl. klin. Wchnschr. 55:417 and 450, 1918.

K. F. Wenckebach (Die Unregelmässige Herztätigkeit und ihre klinische Bedeutung, Leipsic, Wilhelm Engelmann, 1914) called attention to the fact that quinine traditionally was supposed to be of value in heart failure. He found that after 1 gm. of quinine fibrillation temporarily ceased in a certain patient (p. 125) but added, "Since this experience I have repeatedly given quinine but have only caused cessation of fibrillation in one patient." However, this observation stimulated Frey to try various quinine derivatives in auricular fibrillation—quinine, quinidine (conchinine), and cinchonine. Quinidine was found most effective in terminating fibrillation; in 8 of 12 cases there was restoration, at least temporarily, to a normal mechanism. Indeed, Frey found that most of his patients soon had a return to fibrillation. He observed however, that the auricular rate was always slowed by quinidine, even though normal mechanism might not be restored, and he described occasional instances of cinchonism—diarrhea and ringing in the ears. Finally, he describes improvement in the clinical condition of patients after normal mechanism was restored. Frey soon presented another paper on the subject (Weitere Erfahrungen mit Chinidin bei absoluter Herzunregelmässigkeit, Berl. klin. Wchnschr. 55:849, 1918), in which he noted termination of the arrhythmia in about half the cases in one to three days, occasional severe reactions to the drug (idiosyncrasy), and the importance, if failure was present, of using digitalis before quinidine. "Cessation of fibrillation depends on reducing irritability in the region of the auricular muscle." Although numerous confirmatory papers (summarized by Levy) soon appeared in German, it was not until R. L. Levy (Restoration of the Normal Cardiac Mechanism in Auricular Fibrillation by Quinidin: Preliminary Report, J. A. M. A. 76:1289, 1921) called attention to the drug that American physicians began to use it. In a later paper, Levy (Clinical Studies of Quinidin: IV. The Clinical Toxicology of Quinidin, J. A. M. A. 79:1108, 1922) discussed the untoward effects of the drug under the following headings: unpleasant symptoms, induction of heart failure, sudden collapse, occurrence of rhythms indicating intoxication of the heart muscle, embolism, and sudden death. This alarming list perhaps scared doctors so that they used the drug carefully, and 35 years later papers were still appearing on the dangers of quinidine (Siegel, S., and Horn, H.: Quinidine Allergy, Am. Heart J. 39:302, 1950; Thomson, G. W.: Quinidine as a Cause of Sudden Death, Circulation 14:757, 1956). Levy felt that exact knowledge of how quinidine abolished fibrillation was not at hand, and it was T. Lewis who in terms of the circus movement theory explained the action of quinidine in fibrillation (The Action of Atropin and Quinidine in Fibrillation of the Auricles, Am. J. M. Sc. 164:1, 1922). Lewis (The Value of Quinidine in Cases of Auricular Fibrillation, Am. J. M. Sc. 153:781, 1922) also gave an early discussion of the therapeutic problems. Since the first papers, innumerable discussions of the use and value of quinidine in fibrillation have been published, most of which add little to the subject.

However, with the development of methods for measuring blood quinidine levels (Brodie, B. B., and Udenfried, S.: Estimation of Quinine in Human Plasma, with a Note on Estimation of Quinidine, J. Pharmacol. & Exper. Therap. 78:154, 1943; Linenthal, A. J.; Ulick, S., and Patterson, L. A.: Fluorometric Measurement of Plasma Quinidine and Its Correlation with Cardiac Effects in Man, J. Clin. Invest. 26:1188, 1947), a new approach to the use of the drug became available. M. Sokolow and A. L. Edgar (Blood Quinidine Concentrations as a Guide in the Treatment of Cardiac Arrhythmias, Circulation 1:576, 1950), for example, found that 75% of patients with auricular fibrillation converted to normal mechanism by quinidine did so at plasma levels between 4 and 9 mg. per liter.

Higher levels were only rarely effective although in one patient a level of 15.8 mg. was required. Sokolow and Ball later (Factors Influencing Conversion of Chronic Atrial Fibrillation with Special Reference to Serum Quinidine Concentration, Circulation 14:568, 1956) summarized their further experience. Average serum quinidine concentration required for conversion was 6.1μg. per milliliter. Eighty-five per cent of successful conversions occurred at serum concentrations of 8μg. per milliliter or less. The whole subject is reviewed in the book by Harry Gold (Quinidine in Disorders of the Heart, New York, Paul B. Hoeber, Inc. [medical book department of Harper & Brothers] 1950) and in the article by W. D. Love (The Basis of Quinidine Therapy, Am. J. M. Sc. 229:89, 1955). Antifibrillatory drugs in general are reviewed by J. R. DiPalma and J. E. Schults (Antifibrillatory Drugs, Medicine 29:123, 1950).

12. Lewis T.; Drury, A. N., and Iliesen, C. C. A Demonstration of Circus Movement in Clinical Fibrillation of the Auricles, Heart 8:361, 1921.

Ever since fibrillation of the auricles was recognized, doctors have been curious about the nature of the disturbed mechanism responsible for the disorder, but for 30 years after 1921 the view that in fibrillation the auricular impulse followed a rapid continuous and circuitous path in the auricle was accepted by all but a very few. The detailed evidence may be read in a large series of papers by T. Lewis and his associates, mostly in the journal *Heart* for the years 1920-1921; we can only list a few high spots. Lewis tells the story of the development of the circus movement theory in his paper (The Nature of Auricular Fibrillation as It Occurs in Patients, Heart 8:193, 1921). It appears that A. G. Mayer, working on a jellyfish, Cassiopea xamachana (The Cause of Pulsation, Pop. Sc. Monthly 73:481, 1908), first demonstrated circus movement.§ "But if we cut out the center of the medusa and also remove the rim, thus forming a ring of tissue without sense organs, this rim remains quiescent in seawater unless we stimulate it at any point . . . with a single momentary touch of a crystal of potassium, or in some other manner, when a contraction wave starts out from the point touched. . . . Then there is only one wave left in the circuit and this travels constantly around for hours or days until something stops it. . . ." C. R. Mines (On Dynamic Equilibrium in the Heart, J. Physiol. 46:349, 1913), in the course of a study on the nature of the response of cardiac muscle to stimulation says: "Provided the transmission in each direction was slow, the chamber at either end would be ready to respond (its refractory phase being short) and thus the condition once established would tend to continue. . . . The experiments I have been able to make have given results in accord with this conclusion." The experiments consisted of preparing a tortoise heart in such a way that strips of auricle were attached to strips of ventricle so as to form a ring. When the favorable circumstances of slow conduction and short refractory period were present a continuous circulating rhythm was set up. "The data provided by the experiments recounted in this paper suggest an explanation of the important and interesting condition of *delirium cordis* or fibrillar contractions"; later he says: "If a closed circuit of muscle is provided of considerably greater length than the wave of excitation, it is possible to start a wave in this circuit which will continue to propagate itself round and round the circuit for an indefinite number of times. . . . It is capable of further extension to explain the condition of fibrillation, which arises under precisely those circumstances which produce the conditions in heart muscle essential for the manifestation of circulating excitation, namely, a slow

§ Mayer's first publication on the subject was as follows: Mayer, A. G.: Rhythmical Pulsation in Scyphomedusae, Carnegie Institution Publication No. 47, 1906, pp. 1-62.

and short wave of excitation. Once started, the high frequency of repetition of the excitations tends to maintain the condition." W. E. Garrey (The Nature of Fibrillary Contraction of the Heart: Its Relation to Tissue Mass and Form, Am. J. Physiol. 33:397, 1914) a little later studied the physiology of the subject further and concluded: "The experiments support the block hypothesis and suggest that the blocks probably result in intramuscular ringlike circuits with resulting 'circus contractions' which are fundamentally essential to the fibrillary process. Such ring circuits can exist in large masses but not in sufficiently small ones." It was the observations of Mines and of Garrey, physiologists, which stimulated Lewis to "endeavor to carry knowledge from the state of hypothesis to that of conclusion." Lewis' final demonstration followed his paper on flutter (A Demonstration of Circus Movement in Clinical Flutter of the Auricles, Heart 8:341, 1921) a disturbance obviously closely related to fibrillation. "A study of the movements of the electrical axis of the auricle confirms in a striking manner the conclusion which has been drawn from experiments on animals, namely that in fibrillation a single circulating wave controls the beating of the auricles. But this central or circulatory wave does not run the constant course which it pursues in flutter. . . ."

A review of early knowledge of auricular fibrillation is that of Garrey (Auricular Fibrillation, Physiol. Rev. 4:215, 1924).

13. Cutler, E. C.; Levine, S. A., and Beck, C. S. The Surgical Treatment of Mitral Stenosis: Experimental and Clinical Studies, Arch. Surg. 9:689, 1924.

The appearance of fibrillating auricles experimentally induced, for example, by electric shocks, had been familiar to experimenters (for example, Cushny, Ref. 6) for a long time. No one knew as yet whether the fibrillation which was postulated in patients presented the same characteristics. T. Lewis tells of a demonstration of spontaneous auricular fibrillation in an old horse (Clinical Science, London, Shaw and Sons, 1934, p. 29). "When the chest of this horse had been incised and opened, an excellently clear view of the beating heart was obtained. The ventricular beating was rapid and grossly irregular. . . . At first no intrinsic movements could be seen in the auricle . . . but close inspection revealed the expected flickering movements upon the surface." A less favorable account of presumably the same transaction was, however, given by Lewis some years before (Ref. 8, p. 348, footnote): "The horse was killed and the chest quickly opened. Unfortunately the right ventricle was damaged during this operation. Inserting the hand into the chest the ventricle could be felt to beat rapidly and irregularly. . . . The ventricle was grasped and drawn through the wound, but fibrillation ensued. The auricle was then seen in a state of fibrillation. . . ."

It was not, however, until 1924 that Cutler, Levine, and Beck gave a graphic description of human auricles in a state of fibrillation in a patient with mitral stenosis in whom they attempted valvulotomy. "The right auricle was enormously dilated, blue in color, and in complete rest, without even fibrillary motions running across it. The right auricular appendage from time to time showed irregular convulsive contractions." The left auricle was similarly immobile. Nowadays (1957), in the lush era of mitral commisurotomy, fibrillating auricles are seen, so to speak, every day.

14. Scherf, D.: Versuche zur Theorie des Vorhofflatterns und Vorhofflimmerns, Ztschr. ges. exper. Med. 61:30, 1928.

But while the "circus movement" theory of fibrillation as sponsored by Lewis was promptly and almost unanimously accepted in the English-speaking world, workers in Germany were much more skeptical. C. J. Rothberger (Neue Theorien über Flimmern und Flattern, Klin. Wchnschr. 1:82, 1922), for example, reviews the whole problem and feels that the evidence is perhaps in favor of multiple foci of impulse formation rather than circus movement, voicing the

opinion of prominent German students. It was D. Scherf, however, who first in Germany and later in America has strictly objected to the circus theory. He found for example that tying the taenia terminalis, which was supposed to be an integral part of the path, stopped flutter in only 1 of 17 dogs. Tying of other bundles of muscle also had no effect. There were various experiments, all of which made Scherf conclude that in flutter and fibrillation there exist high-frequency heterotopic foci of irritation, a condition which is not clearly separable from other tachycardias. Scherf, with F. J. Romano and R. Terranova (Experimental Studies on Auricular Flutter and Auricular Fibrillation, Am. Heart J. 36: 241, 1948), later produced auricular tachycardia with a rate of 200-400 per minute by injecting aconitine into the region of the head of the sinus node (Studies on Auricular Tachycardia Caused by Aconitine Administration, Proc. Soc. Exper. Biol. & Med. 64:233, 1947). "Cooling of the focus of injection immediately abolishes the fibrillation which reappears when the cooling is interrupted. These results can not be explained by the circus movement theory of Lewis. They can only be explained by assuming that auricular flutter and fibrillation are initiated by rapid impulse formation in a single center." Still further experiments (Scherf, D., and Terranova, R.: Mechanism of Auricular Flutter and Fibrillation, Am. J. Physiol. 159:137, 1949) seemed to Scherf to fit in with his views, and in 1953, with A. I. Schaffer and S. Blumenfeld (Mechanism of Flutter and Fibrillation, A. M. A. Arch. Int. Med. 91:333, 1953), he reviewed the whole subject and stated his final conclusions: "The state of fibrillation is characterized by the presence of innumerable tachysystolic centers of both large and small degree. The theory is based on the presence of minute electrical oscillations in fibrillating muscle. They are small, rapid and ubiquitous and therefore not manifestations of conducted impulses. They must arise in situ, and they thus constitute tachysystolic foci."

In 1953 a number of American authorities (H. Hecht, L. N. Katz, A. Pick, M. Prinzmetal, and A. Rosenblueth) were brought together in a symposium to discuss the question of whether circus movement of the auricular impulse did or did not explain the mechanism of auricular flutter and fibrillation (The Nature of Auricular Fibrillation and Flutter: A Symposium, Circulation 7: 591, 1953). Opinions were somewhat divided.

15. Prinzmetal, M.; Oblath, R.; Corday, E.; Brill, I. C.; Kruger, H. E.; Smith, L. A.; Fields, J.; Kennamer, R., and Osborne, J. A. Auricular Fibrillation, J. A. M. A. 146:1275, 1951.

Although Scherf had consistently opposed the circus movement theory, it was the work of Prinzmetal and his associates which really aroused interest in the problem among American workers, Prinzmetal working with the aid of methods used by the motion picture industry, photographed fibrillating auricles by high-speed cinematography. By this method he was able to observe the contractions of the auricle in "slow motion" and convinced himself that these were incompatible with the circus movement theory. Electrical activity of the auricles was also recorded with the cathode-ray oscillograph. These records he also felt were incompatible with circus movement. Fibrillation, in brief, he concluded, "represents an advanced degree of conduction failure which occurs when the rate of discharge from the ectopic focus is too rapid to permit adequate conduction recovery in the auricle between successive contraction and excitation processes." The views of Prinzmetal and his associates were soon embodied in a handsome volume (Prinzmetal, M., et al.: The Auricular Arrhythmias, Springfield, Ill., Charles C Thomas, Publisher, 1952). A further study with emphasis on auricular fibrillation in man as seen at mitral commisurotomy was published later (Prinzmetal, M.; Rakita, L.; Bordnas, J. L.; Flamm, E., and Goldman, A.: The Nature of Spontaneous Auricular Fibrillation in Man,

J. A. M. A. 157:1175, 1955) "These direct methods of observation revealed a chaotic disturbance of auricular activity unlike anything seen during other arrhythmias. The fibrillation consisted of heterorhythmic large and small waves occurring simultaneously at rapid and irregular rates. No circus movement was found. . . ."

16. Lewis, J. K. Auricular Fibrillation for Many Years with Spontaneous Reversion to Sinus Rhythm: Report of 3 Cases, Stanford M. Bull. 13:131, 1955.

While paroxysmal auricular fibrillation is well recognized (Parkinson, J., and Campbell, M.: Paroxysmal Auricular Fibrillation: A Record of 200 Patients, Quart. J. Med. 24:67, 1930; Master, A. M., and Eichert, H.: Functional Paroxysmal Auricular Fibrillation, Am. J. M. Sc. 211:336, 1946), when the disturbance has been established for any length of time spontaneous reversion to a normal mechanism is not to be expected. Lewis, however, reports three patients with severe heart disease in whom return of normal mechanism was verified electrocardiographically after the disturbance had been present for 17 years in one case and 11 years in the other two. Lewis also refers to the very few cases in the literature.

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Contributions of Basic Science to Modern Medicine

Aldosterone

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Four hormones originating in the human adrenal cortex account for almost all of its recognized biological effects. Some 10 to 20 mg. of hydrocortisone, secreted daily in normal man, affects organic metabolism and numerous related "glucocorticoid" functions; 0.2 to 0.4 mg. of aldosterone, released under ordinary conditions, affects predominantly the balance of sodium and potassium. Small amounts of corticosterone and of 11-oxygenated 17-ketosteroids are also secreted by the adrenal. All of these substances have been recovered from adrenal cortical extracts, from media in which adrenal tissue or homogenates have been incubated, and from adrenal vein blood. Other substances with interesting biological properties doubtless originate in the adrenal cortex under abnormal conditions. Although a number of natural or synthetic steroids have appreciable mineralocorticoid activity, bioassays of adrenal incubates, extracts, adrenal effluent blood, or urine indicate that aldosterone accounts for the largest part of the sodium-retaining and potassium-excreting activity present in normal adrenal secretions.[1,2]

When doses of aldosterone as small as 100μg. are administered to patients with Addison's disease, sodium excretion is reduced.[3-5] If quantities approaching 1 mg. per day are given in divided doses for several days, there is weight gain, and eventually edema may appear. Potassium excretion is increased, especially at higher doses. A convenient measure of the activity of aldosterone is the increase of potassium-to-sodium ratio in the urine. Increase in this ratio reflects secretion of potassium into the renal tubule, accompanied by sodium reabsorption, under the stimulus of mineralocorticoid hormones.

In addition to these actions on electrolyte balance, which are useful in the treatment of Addison's disease, aldosterone has a number of other actions. It seems possible that some of these may lead to therapeutic applications. Only when more hormone is available for extensive testing will its place in therapy be more fully explored.

The evolution of our knowledge of aldosterone has been extensively reviewed in other places.[6-8] It had been known that mineralocorticoid activity existed in adrenal cortical extract which could not be accounted for by the quantities of hormones known to be present. The active substance was elusive because of the minute amount of material present and its ease of destruction by chemical methods then in use. The isolation of this hormone followed development of a sensitive bioassay, which indicated the presence of highly active material in adrenal cortical extract and in human urine, and the application of partition chromatography,

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Because of limitations of space, only a small fraction of relevant literature is included in the bibliography. Additional references will be found in these original publications and reviews.

which allowed separation from the other corticoids with a minimum of loss. Identification of the unique structure of aldosterone resulted from a remarkable combined effort of experts in related fields.[9]

Measurement of Aldosterone

The investigator and physician must recognize the limitations of current methods in order to plan and interpret his results. Measurement of aldosterone in blood plasma is not practicable under ordinary conditions.

Aldosterone, like other adrenal hormones, is thought to be largely reduced in the liver to a "biologically inactive" form, which is excreted by the kidneys. Only the minute amounts of the "unchanged" biologically active hormone excreted in urine are measured by current methods. The hormone must be protected by freezing the urine as soon as possible after collection. The quantity of hormone recovered varies greatly with different forms of hydrolysis and extraction.[10] Since the largest yield can be obtained by repeated extraction of urine held at pH 1.0 to 1.5 for at least 24 hours, this is the preferred method. It is desirable to wash the extract with cold dilute alkali and water. Paper chromatography allows the separation of aldosterone from other substances which migrate at different rates in the system selected. However, no single system of chromatography permits the isolation of aldosterone from all other substances which may have interfering chemical or biological properties. If the material is to be purified, repeated chromatography is necessary, with careful selection of different systems. Since some material is lost during each step even with careful technique, the measurement of refined material may not reflect in any systematic way the quantity of material initially extracted from the urine.

Biological assay is necessary for the detection and estimation of normal or subnormal amounts of aldosterone in urine (Table 1). When aldosterone output is above 5μg. or 10 μg. per day, chemical estimation is practicable, provided that loss and contamination are minimized by careful technique.[11] For measurement of extracts containing 20μg. or more of aldosterone, a chemical method is generally more appropriate. The quantity of hormone present is estimated by ultraviolet light absorption and tetrazolium reduction after separation in two or more chromatograms. It is only after long practice and constant use that either bioassay or chemical estimation becomes reasonably reliable. Both of these methods are so difficult and laborious as to be technically and economically unfeasible in the usual clinical laboratory.

Estimates of Aldosterone Extracted from One Day's Urine *

	Biological Assay, μg./Day	Physico-Chemical, μg./Day
Normal men and women		
Ordinary diet	1–7 (mean 2–3)	1–10 (mean 3–5)
Low-sodium diet (10 mEq.)	10–60	9–44
Severe sodium depletion	100–300	--
After sodium load (400 mEq.)	0	†
Low-potassium diet (9 mEq.)	0–0.5	†
After potassium load (200 mEq.)	2–6	--
(300 mEq.)	--	5–15
Normal pregnancy (28–40 wk.)	15–30	0.5–110
Nephrotic syndrome	10–200	--
Congestive heart failure	10–55	5–55
Cirrhosis with ascites	12–200	10–120
Idiopathic edema	7–320	66–123
Tumor of adrenal cortex (mineralocorticoid excess)	8–200	5–34
Adrenal insufficiency or bilateral adrenalectomy	0	†
Hypopituitarism	2–3	--
Hypophysectomy	0.5–2	7
Sodium-losing nephritis	10–300	--

* Repeated or continuous extraction after acidifying to about pH 1.5. Representative data are given to indicate commonly observed range in each group but not to imply that all cases fall within this range.

† Method not suitable for detection of very small quantities. References to original sources of data may be found in the text. Biological assays were performed at McGill and Stanford Universities and National Heart Institute. Physicochemical estimations were made at Ciba Research Institute at Basle, Geneva Cantonal Hospital, Munich University Clinic (I. Med.), Peter Bent Brigham Hospital, and Hotel-Dieu Hospital of Montreal.

Errors of interpretation may arise if these methods are used without full recognition of their limitations. For example, it has been stated on the basis of chemical determinations that increased levels of aldosterone do not appear in the urine of normal men during the first days of sodium deprivation. A more exact statement would be that the methods used did not detect the rise in aldosterone, which has been demonstrated by more sensitive methods to occur very early in the course of sodium deprivation.

Recent studies suggest that aldosterone is reduced by the liver to a form analogous to "tetrahydrocortisone." This metabolite appears in the urine after administration of aldosterone or during periods of increased aldosterone excretion. The separation and measurement of aldosterone metabolites deserve further attention, since there should be much larger amounts of the metabolite than of the biologically active hormone in the urine. Advantage may be taken in this case of the specific chemical structure of the aldosterone metabolite, and one may hope that this will lead to a simplified chemical method of measurement. It will be important to recognize that previous data on free aldosterone excretion in urine will not necessarily be carried over directly into the interpretation of the levels of metabolite in the urine. Experience with metabolism of hydrocortisone in liver disease or hypothyroidism would suggest that when the rate of metabolism of a hormone is decreased, a smaller quantity of secreted hormone can maintain normal blood levels.

Diurnal Variations

It is conventional to collect urine during one full day for extraction of aldosterone. Under these circumstances, certain correlations are evident between the daily output of aldosterone and the electrolyte and fluid balance of the patient. When collections are made for less than one full day, the diurnal variation in aldosterone excretion must be taken into account. The output of biologically active hormone in the urine is generally much higher in the morning and midday than in evening or overnight specimens. This diurnal rhythm of aldosterone secretion usually resembles the rhythm of hydrocortisone secretion, but the cycles may vary independently when the subject undergoes varying environmental stresses. Figure 1 shows diurnal variations observed in four normal persons. In the fourth case, two cycles are shown: (1) represents a pattern observed during a period of disturbed sleep and nocturnal activity following the advent of a healthy infant in the home, while (2) shows the pattern after the household had returned to its usual schedule.

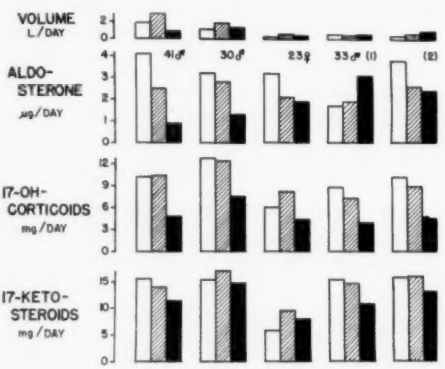

Fig. 1.—Diurnal variations in aldosterone and metabolites of other adrenal hormones in urine. Collections from 7 a. m. to 3 p. m. are indicated by open blocks. Shaded blocks indicate excretion from 3 p. m. to 11 p. m., and solid blocks, from 11 p. m. to 7 a. m. Collections from the same 8-hour period on three successive days were pooled, and the results are expressed as quantities excreted per 24 hours.

Sodium and potassium excretion also tend to be higher during the day than at night. The ratio of potassium to sodium in urine seems to be related to aldosterone output in the cases studied. The diurnal cycle of sodium and potassium excretion in the urine may be modified by many factors, including posture, exercise, meals, and sleep, whose effects on sodium excretion have not been shown to depend on changes in adrenal cortical secretion, although some circulating adrenal hormones must be present. Until these matters have been systematically investigated, the interpretation of aldosterone output over periods less than 24 hours will remain uncertain.

Physiologic Control of Aldosterone Output

Some years before aldosterone was isolated and identified, Peters proposed the physiological role of a hypothetical mineralocorticoid.[12] He suggested that in normal man the sodium-retaining mechanism, mediated by adrenal cortical secretion, is sensitive

to changes of extracellular fluid volume. The osmolarity of the fluid is maintained during alterations in sodium balance by appropriate changes in antidiuretic hormone secretion by the posterior pituitary. Borst [13] pointed out that acute or diurnal changes of sodium excretion were to some extent independent of the slower adjustments of extracellular fluid volume. It is with the larger and slower changes that the studies of aldosterone have been chiefly concerned, for reasons which have been pointed out.

Effects of Sodium and Water Balance

The output of aldosterone in normal man is most readily affected by measures which change the body sodium content.[14] Sodium deprivation, sweating, or diuretics decrease body sodium and increase aldosterone output. Ingestion of excess sodium chloride depresses the output of aldosterone as sodium and water are retained (Fig. 2). Change in body water has an effect like that of body sodium (Fig. 3). Administration of excess water and vasopressin is followed by overhydration, decreased output of aldosterone, and increased sodium excretion in urine.[15] Marked dehydration results in some increase of aldosterone and decreased urine sodium excretion, even when sodium loss is insignificant. These observations can not be explained by changes in serum sodium concentration. Aldosterone secretion appears to be stimulated by reduction of extracellular volume or inhibited by an excess of extracellular fluid in normal man. If aldosterone regulates the excretion of sodium, this arrangement acts to stabilize extracellular fluid volume. Water excretion is adjusted to preserve constant osmolarity and extracellular sodium concentration with the aid of hypothalamic receptors and posterior pituitary secretion of vasopressin.

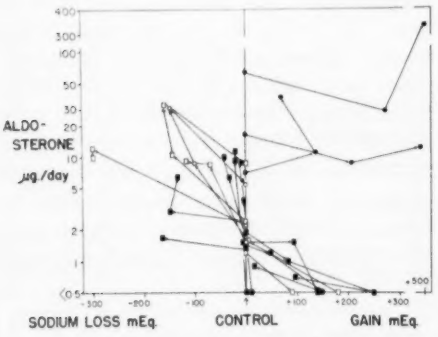

Fig. 2.—Output of aldosterone during sodium gain or loss following alterations in sodium or potassium intake. Three groups of subjects are shown. Open squares show normal men and women given diets of varying sodium content; sodium deprivation (10 mEq. per day) is followed by loss of sodium and increased aldosterone, while loading with sodium chloride (300-400 mEq. per day) is followed by moderate sodium retention and disappearance of aldosterone from urine. Solid squares show normal men with various intakes of potassium; high potassium intake (200 mEq. per day) is associated with loss of sodium with slight to moderate increase of aldosterone. Potassium depletion (9 mEq. diet) leads to sodium gain and diminished aldosterone, which are reversed by sodium deprivation; subsequent potassium replacement leads to a sharp rise in aldosterone, with little change in external sodium balance (steeply rising solid squares near center "control" line). Solid circles at upper right show abnormal persistence of high aldosterone output in idiopathic edema during sodium chloride loading, with retention of unusually large amounts of sodium in the body.

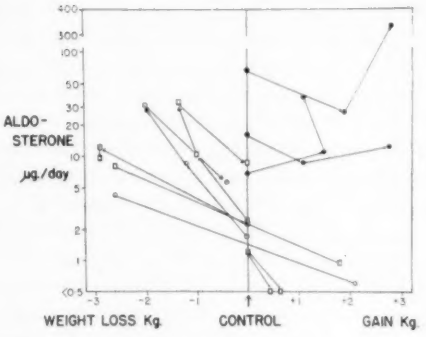

Fig. 3.—Output of aldosterone during weight gain with sodium loading or weight loss on sodium deprivation. Normal subjects are indicated by open circles and squares; patients with edema, solid dots.

It is still not clear how these changes of volume are detected and how they lead to stimulation of the adrenal cortex. Blood plasma occupies a central position in the extracellular fluid volume. Acute removal of a large volume of blood is followed by increased aldosterone secretion in the dog [16] and moderate rise of urine aldosterone in man. The effects of moderate hemorrhage

have not been consistent or impressive in a few subjects studied here, and published data have not yet shown that altered blood volume accounts for many observed changes in aldosterone. Expansion of plasma volume with iso-oncotic albumin has little effect on sodium excretion, and hyperoncotic albumin may actually decrease the excretion of sodium in normal subjects. Cerebrospinal fluid pressure is probably not an important factor in the control of aldosterone secretion.[17]

Observations in various diseases, in which cardiac output, blood volume, or extracellular fluid volume are altered, present no consistent relationship between these functions and aldosterone output or sodium balance. If volume or flow is detected by the stretch of a receptor in an auricle or artery or other single site, these apparent discrepancies might be explained. Recent observations [18] have pointed to the diencephalon as a possible site of the reception or transmission of impulses regulating aldosterone secretion. A humoral factor may be responsible for stimulation of aldosterone secretion, but the source and nature of this factor are unknown. It may be of interest that secretion of aldosterone in vitro by isolated rat adrenal glands is stimulated by a protein fraction of human plasma.[19]

Effects of Potassium and Ammonium Salts

Administration of potassium salts generally increases the output of aldosterone.[20] The rise in aldosterone which follows potassium loading is not as striking or consistent as that after sodium deprivation. In some cases the effects of potassium can be related to loss of sodium and possible diminution in extracellular fluid volume, but in other normal subjects, sodium loss does not appear to be a determining factor, though no direct measurements of extracellular volume were made.

In potassium deficiency, aldosterone secretion may be depressed.[21,22] Some sodium retention occurs during potassum depletion, but it is not clear whether extracellular volume is regularly expanded. Figure 2 indicates that the fall in aldosterone in subjects given a low-potassium regimen follows a pattern not unlike that seen in sodium-loading experiments. When potassium-depleted subjects are deprived of sodium, the rise in aldosterone and the fall in sodium in urine are delayed. Potassium loading at the end of a period of sodium and potassium deprivation results in a sharp increase in aldosterone output without appreciable loss of sodium or water from the body. These observations suggest that potassium deficiency has some effect on aldosterone secretion in addition to its effect on sodium and water balance.

When large amounts of potassium salts are given to a sodium-depleted dog or man, serum potassium and aldosterone output increase impressively, and a correlation between these two measurements can be demonstrated.[23] On the other hand, when normal subjects are deprived of potassium, aldosterone output falls, and it rises again when potassium is returned to the diet, without notable change in serum potassium. Sodium deprivation induces large changes in aldosterone with only minor changes in serum potassium. In normal subjects given diets of widely varying electrolyte content

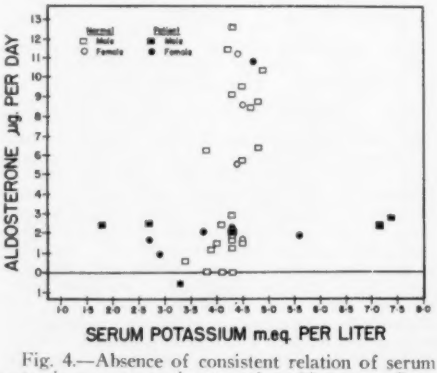

Fig. 4.—Absence of consistent relation of serum potassium concentration to urine aldosterone. Data from normal subjects on different intakes of sodium and potassium are shown by open circles and squares. Solid dots indicate measurements in patients with various disorders not ordinarily associated with altered aldosterone output.

and in patients showing a wide range of serum potassium concentration, no systematic relationship between serum potassium concentration and aldosterone output is evident (Fig. 4). These observations suggest that extracellular potassium concentration does not exert a large influence on aldosterone secretion.

Potassium deficiency and loading affect intracellular potassium stores more than the small fraction in extracellular fluid. Potassium excretion seems to be regulated primarily by intracellular potassium. It is possible that adrenocortical steroidogenesis is modified by potassium content of adrenal tissue. This could scarcely account for aldosterone increases, initiated by altered body sodium, which occur without changed external balance of potassium.[24]

An effort has been made to relate aldosterone output to the grossly altered body composition in disease. A small group of patients with stationary or decreasing edema were studied while taking a diet low in sodium and potassium.* No consistent relation between exchangeable potassium (K_E) or sodium (Na_E) and aldosterone is evident, but the ratio, K_E to Na_E, seems to vary directly with aldosterone excretion (Fig. 5). When similar ratios in normal men on widely varying intakes of sodium and potassium are calculated from normal values and changes in external balance, a parallel relation of aldosterone and K_E: Na_E is evident. Although the ratio represents two separate components, K_E and Na_E change in opposite directions under the influence of aldosterone (as well as in several forms of disease), and each component may affect aldosterone output, though possibly by different mechanisms.

It is possible that acidosis may stimulate aldosterone secretion. The data are not easy to interpret because of the interaction of hydrogen, potassium, and sodium ions in cellular exchanges and renal excretion. Administration of ammonium chloride to a normal man depleted of sodium and potassium is followed by a striking rise in aldosterone without significant effect on external balance of sodium or potassium.[21] It has been suggested that mineralocorticoids enhance renal tubular reabsorption of bicarbonate, which is usefully increased in acidosis.

* M. P. O'Meara, L. W. Birkenfeld, F. A. Gotch, and I. S. Edelman measured Na^{24}, K^{42}, and D_2O distribution in these patients (*J. Clin. Invest.* 36: 784, 1957) and allowed us to use their data for these calculations.

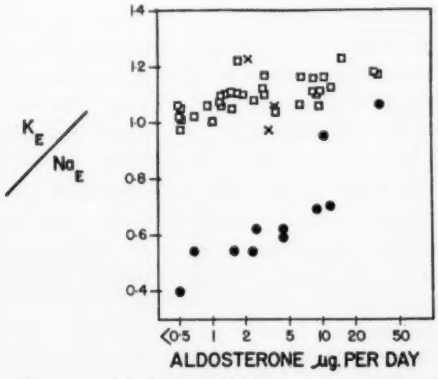

Fig. 5.—Relation of aldosterone to ratio of exchangeable potassium to sodium. Normal subjects are indicated by open squares; edematous patients, solid circles; patients without edema, crosses.

Corticotropin and Stress

Corticotropin secreted by the anterior pituitary is necessary for maintenance and stimulation of normal adrenal secretion of hydrocortisone and corticosterone but is less important in the regulation of aldosterone secretion.[7,22] Hypopituitarism is not ordinarily associated with reduced aldosterone in urine.[53] Subjects receiving prolonged corticotropin (ACTH) therapy may excrete very high levels of hydrocortisone metabolites simultaneously with a normal output of aldosterone. However, there is a brief rise in aldosterone when corticotropin is first given. This initial rise may be greater in patients who are taking a low-sodium diet.[15]

After surgical operations, there is frequently a rise in aldosterone output.[25] This varies a good deal in extent and in time of appearance. It is difficult to be certain how much of this increase is the consequence of

loss of fluid and electrolyte, of blood loss, and of other factors which might create circulatory insufficiency or of the endogenous secretion of corticotropin following surgery. Furthermore, it is difficult to assess the role of aldosterone in postoperative electrolyte alterations in the presence of marked rises in other adrenal cortical hormones, as well as changes in circulation and renal function.

Aldosterone output rises after air encephalography.[17] On the day of encephalography, spontaneous intake of food and fluid is usually much reduced. There is a fall in urine volume and sodium content, while no consistent change in potassium excretion is seen. Both aldosterone and 17-hydroxycorticoids in urine increase approximately twofold. When water and electrolyte intake are maintained at control levels by intravenous fluids on the day after encephalography, urine sodium output returns to control levels but decreased water excretion and increased potassium excretion remain. Aldosterone and 17-hydroxycorticoids in urine are increased even when intake of fluid and electrolyte is maintained. This pattern resembles the changes which follow administration of exogenous corticotropin and might reasonably be attributed to increased endogenous secretion of corticotrophin.

Aldosterone, Sodium Retention, and Edema

Measurable amounts of fluid escape from capillaries when venous pressure is raised acutely or when the colloid osmotic effect of plasma proteins is reduced. Nevertheless, it is not always easy to explain the appearance or relief of edema on the basis of venous pressure or plasma proteins. Changes in renal excretion of sodium play a leading role in the collection or removal of edema. Diminished renal blood flow may accompany sodium retention in some cases, but in other instances, blood flow and glomerular filtration rate are normal. The antidiuretic hormone, vasopressin, has little immediate effect on sodium excretion. The moderate water retention which follows continuous administration of vasopressin is generally followed by sodium loss through the kidneys.

In patients with Addison's disease, accidental overdosage with deoxycorticosterone reduces urine sodium excretion sharply and is often followed by weight gain and accumulation of edema. In some instances, not only dependent edema but other signs and symptoms of congestive heart failure appear. These clinical observations stimulated a search for possible sodium-retaining hormones. Biological assay showed that increased sodium-retaining activity is present in patients with diseases of heart or liver during accumulation of edema.[26] It soon became apparent that a similar substance, different from previously known adrenal hormones, was secreted by the adrenal cortex.[1] After the identification of aldosterone from adrenal cortical extract,[9] crystalline material of identical nature was obtained from urine of patients with the nephrotic syndrome and with congestive cardiac failure.[27,28] The sodium-retaining activity of lipid extracts of urine of these patients appears to be due solely to aldosterone.

Adrenal Hormones in Nephrotic Syndrome and Hypoproteinemia

Early studies showed that the sodium-retaining capacity of the urine in the nephrotic syndrome was sharply reduced when diuresis was induced by administration of cortisone or corticotropin.[26] At such times, not only was the sodium-retaining activity of the urine reduced, but comparable fractions from the urine might actually promote diuresis, giving rise to the suspicion that a "sodium-losing hormone" might also exist. Reduction in aldosterone excretion could also be accomplished by injection of concentrated human serum albumin into some of these hypoproteinemic and hypovolemic persons, but aldosterone output fell only when the treatment was successful in inducing diuresis.[29] In other patients, the

administration of cortisone or albumin was without effect either on the disease or on the output of aldosterone, which remained high while hypoproteinemia and edema persisted. The output of aldosterone was highest during the stage of accumulation of edema. Somewhat lower levels were noted during static maintenance of edema, while sodium-retaining activity disappeared entirely during diuresis.

The relationship between high aldosterone output, low sodium excretion, and increasing edema is most readily demonstrated early in the course of the nephrotic syndrome. In cases of longer duration, other factors must contribute to the inadequacy of sodium excretion, which does not regularly return to normal when aldosterone output falls spontaneously or after administration of amphenone (1,2-bis-[*p*-aminophenyl]-2-methyl-1-propanone dihydrochloride) (Fig. 6).

Improved water excretion and correction of hyponatremia frequently precede effective urinary excretion of sodium during treatment of nephrosis with cortisone or corticotropin. It has recently been recognized that corticosteroids may improve water excretion in other forms of edema, also. Prednisone has been recommended because of its relatively minor sodium-retaining action. In patients with intractable cardiac

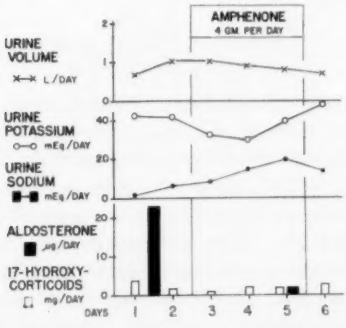

Fig. 6.—Administration of Amphenone to edematous patient with nephrotic syndrome. Note marked fall in aldosterone excretion (bioassay), modest but definite increase in urine sodium, and decrease in urine potassium. Creatinine clearance was reduced to less than one-third of normal in this patient.

failure, cautious administration of prednisone may be followed by diminution in aldosterone excretion and improved effectiveness of diuretics, as well as improved water excretion and correction of hyponatremia.[30] In cirrhosis with ascites, also, prednisone may be helpful in elimination of fluid in selected cases.[31]

Congestive Heart Failure

In congestive heart failure, accumulation of edema is associated with high aldosterone levels and reduced sodium in urine.[10] The physiological disturbances in heart failure are complex, and it would be an oversimplification to imply that aldosterone is the sole or invariable cause of sodium retention. Abnormalities of peripheral hemodynamics and capillary exchanges, renal blood flow, and glomerular filtration rate may all play a part, although no single one of these controls renal sodium excretion. Experimental heart failure in dogs, like its human analogue, is accompanied by increased sodium reabsorption by the renal tubule, which is not adequately explained by reduced glomerular filtration.[32] Removal of the adrenal glands of dogs prevents the sodium retention of heart failure.[33] Administration of deoxycorticosterone under these conditions is followed by sodium retention and edema. These observations suggest that a sodium-retaining factor arising in the adrenal cortex is necessary for the development of edema in congestive failure.

Adrenal function is usually normal in patients with heart disease who are not collecting edema with a normal diet. Increased aldosterone output is associated with "right-sided" heart failure.[34] There is little increase in aldosterone with congestion of the pulmonary circulation alone, but when general edema and ascites appear, the aldosterone output rises. The highest levels are seen in patients with intractable edema and very low urine sodium.

High aldosterone levels in heart failure may decline somewhat after sodium loading.[15,35] When compared with normal per-

sons, however, more sodium chloride must be given, more extracellular fluid is retained, less sodium is excreted, and aldosterone usually does not disappear from the urine in heart failure. The difference between the range of K_E:Na_E ratios in Figure 5 suggests that the response to potassium deficiency and sodium retention in edematous patients is parallel to normal but that much greater alterations in body electrolyte content are tolerated in edema without suppression of aldosterone. One can speculate that the excess of extracellular fluid fails to repair the defect of fluid distribution or hemodynamics which stimulates aldosterone secretion, but we must learn more about control of aldosterone secretion before these phenomena can be defined.

Sodium depletion by diet, diuretic, or ion-exchange resin varies in its effect on heart failure. In patients with intractable edema, aldosterone output increases, and sodium excretion is ineffectual. In less severe cases, especially when combined with rest and digitalis, the patient may respond well, with relief of symptoms and signs of congestion and with adequate diuresis of salt and water, which persists even after diuretic therapy has stopped. In these latter cases, aldosterone output tends to fall toward normal during sodium elimination. This result is opposite to that seen after sodium deprivation and use of diuretics in normal subjects and suggests that the abnormality which stimulates aldosterone secretion has been improved by the diminished congestion and edema.

The concentrations of sodium in sweat, saliva, and stool are reduced when high aldosterone levels occur in adrenal tumor, heart failure, and some related conditions. It is evident that not only the renal tubules but other structures are called on to conserve sodium in these cases. These findings help to account for the limited effectiveness of ion-exchange resins in removing sodium from patients with refractory edema.

Diseases of Liver

Aldosterone excretion is increased during accumulation of ascites in patients with cirrhosis of the liver.[36,37] In these patients with normal glomerular filtration rate, it appears likely that aldosterone is responsible for sodium retention. It is not easy to decide whether this increase in sodium-retaining hormone initiates or follows the collection of extracellular fluid into the abdominal cavity in the initial stages. When ascites is being accumulated, it is evident that an abnormal fraction of the retained salt and water is diverted into the peritoneal cavity and that the administration of sodium to such subjects does not suppress aldosterone output as it does in normal man. On the other hand, sodium restriction, the use of diuretics, or paracentesis usually increases aldosterone output.

Patients with hepatitis may show a transitory increase in aldosterone excretion at the height of their disease. In general, patients with liver disease have higher levels of aldosterone than comparable patients with edema due to other causes. This may possibly be due to diminished inactivation of aldosterone in the liver, so that a higher proportion of the secreted hormone appears in the urine in biologically active form. More definitive information on this may be secured when it becomes possible to measure metabolites in the urine.

Idiopathic Edema with Hyperaldosteronuria

Patients have been described who had edema without obvious explanation other than a high aldosterone excretion.[38,39] We [40] have studied a series of 15 women between the ages of 33 and 61 years, generally intelligent and conscientious persons living and working under some strain and having symptoms of tension and emotional lability. These patients showed edema which fluctuated with environmental factors, fatigue, and emotional reactions. This edema was not related to the menstrual cycle, although some exacerbation might occur with

the menses. Five of these patients had dysuria and other complaints referred to the bladder without objective urological abnormality. One patient suffered from vertigo, and in another instance papilledema was noted. There was a history of obesity or unusual weight loss before the onset of edema in several of these patients. Edema could be eliminated by diuretics or low-sodium diet, at least for a time, but any relaxation of the sodium restriction was followed by weight gain and return of edema. In most of these patients, arterial pressure was normal, and venous pressure was not increased. A few dilated superficial leg veins were noted in some instances, but no evidence of obstruction of the deep veins was present. There was no evident abnormality of heart, circulation, thyroid, liver, or kidneys. The blood was normal both on hematologic and on chemical examinations.

The output of 17-ketosteroids and 17-hydroxycorticoids was not remarkable, but high aldosterone output was associated with weight gain and edema. Instead of the normal suppression of aldosterone output after heavy loads of sodium chloride, several of these patients showed increased aldosterone excretion (Fig. 2). The administered sodium was not excreted in the urine. When judged by the relation of electrolyte excretion to aldosterone output, these patients appear to be less sensitive than normal subjects to endogenous aldosterone. It seems likely that aldosterone excess is involved in the genesis of their edema.

In the absence of any adrenal enlargement demonstrable by tomograms, we have not subjected our patients to surgery. However, other cases have been reported in which removal of one or both adrenal glands has resulted in temporary improvement.[39] Although some morphologic changes in the adrenals have been noted at surgery in several instances, there is no evidence that a discrete cortical tumor was responsible for the excess of aldosterone. At the present time, adrenalectomy should be considered only as a last resort.

These patients present a well-defined syndrome, which can be recognized by history and examination. Although it is possible that there may be more than one cause of the condition, no obvious reason for aldosterone excess exists in most of these instances. In the absence of adrenal tumor, we must infer some persistent stimulus to secretion of aldosterone. Emotional stress and anxiety, which can increase the output of aldosterone in normal subjects,[41] appear to be important precipitating causes of the syndrome in these patients. It seems likely that aldosterone secretion is regulated by a mechanism, part of which is located in the nervous system. It is conceivable that anxiety and tension may "overflow" into this mechanism in a manner analogous to the effect of emotion on water diuresis.

Pregnancy

Aldosterone excretion in increased in normal pregnancy, rising to levels of 15μg. to 30μg. or more in the third trimester. Observations on toxemia of pregnancy at first suggested that the sodium-retaining tendency in this condition might be accounted for by increased aldosterone output. However, it is now generally agreed that aldosterone output is not greater in toxemia than in normal pregnancy.[42] The output of other corticoids is also considerably increased in late pregnancy. If progesterone and its metabolites promote the excretion of sodium,[43] the increase of aldosterone in pregnancy may represent an effort toward compensation. It is perhaps significant that in pregnancy, as in epidemic hepatitis, no correlation has been found between elevated aldosterone output and sodium retention or potassium depletion. These observations support the idea that interfering substances or relative refractoriness to aldosterone may exist.

Hypertension

Large doses of deoxycorticosterone, hydrocortisone, or other potent adrenal hormones, given for some weeks, can cause

an increase in blood pressure in susceptible subjects. There is reason to believe that an excess of aldosterone may also result in elevated arterial pressure, even though most patients with high aldosterone levels are normotensive.

Hypertension is frequently present in cases of adrenal hyperplasia or tumor secreting aldosterone and other cortical hormones. Other typical findings are discussed subsequently. When the tumor is removed, blood pressure usually falls toward normal, when a normal level of adrenocortical secretion is resumed.

A number of patients with severe, benign, essential hypertension excrete somewhat increased levels of aldosterone, which are not satisfactorily explained by diet or congestive heart failure.[44] The results of adrenalectomy in such cases are less impressive than the relief which follows removal of a functioning tumor. In severe hypertension without adrenal cortical tumor, bilateral total or subtotal adrenalectomy is necessary in order to reduce arterial pressure effectively. Corticosteroid replacement is limited to a narrow range to avoid symptomatic adrenal cortical insufficiency with lower dosage or a return of hypertension with higher doses. The blood pressure in essential hypertension appears to be unusually sensitive to corticosteroids, suggesting that adrenal cortical secretions are necessary to maintain arterial pressure but that other factors play a major role.

Syndrome of Mineralocorticoid Excess

Certain patients with adrenal adenoma, carcinoma, or hyperplasia show arterial hypertension and signs of potassium depletion without other evidences of hyperadrenocorticism.[45] Retention of sodium is not usually clinically obvious as edema, although heavy edema may occur. In the mildest cases, there are no symptoms.[46] Headache, dyspnea, cardiac failure, renal failure, or cerebral vascular accident can develop later. Hypokalemia, often with alkalosis, may lead to muscle weakness, periodic paralysis, loss of deep tendon reflexes, paresthesia, and cramps. The electrocardiographic changes of potassium deficiency are sometimes confused with those of left ventricular hypertrophy but are corrected after effective potassium replacement.

The nephropathy resembles in some respects that seen in other forms of potassium depletion. There is loss of concentrating power, even when vasopressin is given. Urine flow may be profuse, suggesting diabetes insipidus. A small amount of protein is found in the urine, and renal function is reduced, although seldom to a serious extent. There seems to be an increased susceptibility to pyelonephritis. Unlike patients with dietary deficiency or loss of potassium through the bowel, patients with mineralocorticoid excess lose potassium in urine and show low titratable acidity, urine pH near 7.0, and an unexpectedly high ammonium excretion.[46,47] In contrast to the hyperchloremic acidosis of renal tubular insufficiency, patients with mineralocorticoid excess often show hypochloremic alkalosis. Whether a selective renal lesion can simulate mineralocorticoid excess in every detail ("potassium-losing nephritis") is doubtful, since most cases so described have turned out to have adrenal hyperplasia or tumor.

When very large amounts of aldosterone were found in the urine of several cases, while 17-hydroxy- and ketosteroids were normal, it seemed logical to attribute this syndrome to "primary aldosteronism." The syndrome may occur in patients with little or no demonstrable excess of aldosterone in the urine.[48] Tumors from patients with this syndrome have been shown to contain and secrete corticosterone or hydrocortisone, which can diminish the sodium-retaining action of aldosterone, while enhancing the potassium-losing effect.[49,50] It is desirable, therefore, to use a less restrictive term than "hyperaldosteronism." A term such as "mineralocorticoid excess" might be broad enough to include all of the human cases with this distinctive syndrome, regardless of hormonal pattern, as well as the replica in-

duced in normal dogs by prolonged overdosage with deoxycorticosterone. There are also mixed forms of the mineralocorticoid syndrome with hyperadrenocorticism of other types.

It has thus become apparent that the measurement of aldosterone in urine is a less reliable diagnostic test than the study of renal function and potassium balance. Given a clinical situation compatible with mineralocorticoid excess, one might find hypokalemia, alkalosis, hypochloremia, and hypernatremia, but, in some instances, these abnormalities are not regularly present. The retention of potassium during the first few days on an intake above 150 mEq. per day gives some idea of the presence and severity of body potassium depletion. Certain typical abnormalities of renal function associated with potassium deficiency are usually present, and nephrosclerosis or pyelonephritis have been described in a number of reported cases. If chronic renal acidosis or other forms of renal disease were present, these might provide an alternative explanation for the metabolic disturbance. Mineralocorticoid excess lowers the concentration of sodium or the ratio of sodium to potassium in sweat, saliva, and feces. Since the adrenal hormones cause far less potassium loss if sodium is not available, some improvement may be apparent with a low-sodium intake. Administration of potassium salts improves hypokalemia and relieves symptoms, although complete replacement of the potassium deficit may not be possible. If these studies give results compatible with mineralocorticoid excess in the absence of other valid explanation, surgical exploration of the adrenal region is indicated.

In most of the reported cases, an adrenal cortical adenoma, often quite small, was found on exploration. In a few cases, carcinoma [51] or bilateral cortical hyperplasia [52] was present. Surgical removal of a tumor was followed by prompt correction of potassium deficiency. Arterial pressure and cardiac and renal function returned slowly toward normal in most cases, but in a few instances of long duration, abnormalities persisted. Renal insufficiency due to nephrosclerosis or pyelonephritis may be aggravated. Early diagnosis and treatment yield superior results in these cases, as always.

Adrenal Cortical Insufficiency

Deficient secretion of aldosterone and other adrenal cortical hormones results in certain clinical patterns, which should be distinguished from other, related, syndromes not related to hypoadrenalism.

In Addison's disease and after surgical adrenalectomy, aldosterone is not detectable in urine.[53] Unless they are adequately treated, these patients are moderate chronic sodium losers, who tend to develop hyponatremia, especially under stress. Serum potassium concentration is likely to be increased.

Measures which cause substantial amounts of aldosterone to appear in the urine of normal man are dangerous in hypoadrenal patients. Sodium deprivation and potassium loading quickly demonstrate the inadequacy of electrolyte regulation in adrenal insufficiency and often precipitate adrenal crisis.

The development of "adrenal crisis" after stress does not prove that adrenal cortical function is completely absent. Some patients with clinical evidences of Addison's disease have a remnant of functioning adrenal cortex which is adequate to maintain normal levels of hydrocortisone in plasma and urine under ordinary circumstances but which fails to respond normally to stress or corticotropin injections.[54] Since aldosterone secretion has not been defined in such cases, inferences based on the assumption that aldosterone is absent in all cases of Addison's disease must be viewed with some reserve.

Certain infants with congenital adrenal hyperplasia suffer from a sodium-losing syndrome. In our experience, this is usually associated with absent to low-normal aldosterone in urine. Increased aldosterone has been noted in some older children.[55] It seems likely that there are a number of different patterns of hormone secretion in congenital adrenal hyperplasia.

Hypopituitarism

"Adrenal crisis" may also develop in patients with hypophyseal or hypothalamic lesions, with impaired function and more or less atrophy of adrenal cortex. In these cases, hydrocortisone secretion is primarily reduced. Significant increases of hydrocortisone in plasma, or of metabolites in urine, after adequate stimulation with an active preparation of pituitary corticotropin is valuable in diagnosis of these cases. Aldosterone output is usually within the range of normal.[53]

Hypophysectomy in animals is usually followed by a small reduction in aldosterone secretion, while hydrocortisone and corticosterone output falls to very low levels.[18,22] In man, hypophysectomy does not depress aldosterone secretion immediately.[39] On the contrary, increased aldosterone secretion is likely to follow hypophysectomy if diabetes insipidus results in loss of body water. Most of these patients tolerate short periods of sodium deprivation and are able to reduce urine sodium to very low levels. Most patients with panhypopituitarism due to disease also tolerate sodium withdrawal without significant clinical disturbance, but a few cases of long standing develop hyponatremia, asthenia, nausea, and other evidences of impending adrenal crisis on the second or third day of sodium deprivation. In two patients who showed this abnormal clinical response, a subnormal rise of aldosterone secretion followed sodium withdrawal, and sodium continued to be lost into the urine. No increase in serum potassium concentration was observed. When hydrocortisone secretion is deficient, impaired diuresis with hyponatremia and symptoms of "adrenal crisis" may develop acutely without significant sodium loss and in the presence of aldosterone.

Other Types of Hyponatremia

It seems likely that impaired diuresis and expansion of body fluids may depress the aldosterone response which ordinarily occurs during sodium deprivation. Thus, certain patients may become "sodium losers" without other evidence of adrenal insufficiency. Persistent sodium loss through the kidneys, with reduced serum sodium concentration but without dehydration, is seen in many seriously ill patients. This "asymptomatic hyponatremia" has been noted in lobar pneumonia, tuberculosis of lungs or meninges, and other conditions. In two cases of bronchogenic carcinoma with metastases, the sequence of impaired diuresis, expansion of body fluids, and reduced aldosterone secretion has been demonstrated.[56] The suggested treatment, water deprivation, may be effective in some instances. We have observed several instances of persistent hyponatremia due to reduced blood volume and impending vascular collapse, corrected after administration of blood or concentrated human serum albumin. Apparently, a number of antidiuretic stimuli can initiate this disturbance.

Renal sodium loss with dehydration may result from renal failure to conserve sodium, for example, in diabetic acidosis, in acidosis due to renal tubular insufficiency, and in "sodium-losing nephritis." In these circumstances, the adrenal cortex responds with a large output of aldosterone, which can only be suppressed by adequate sodium replacement and rehydration.

Hyperkalemia

A high serum potassium concentration may occur in various conditions unrelated to adrenal cortical failure, such as renal insufficiency, oliguria, and acidosis. Heavy potassium loads, endogenous or exogenous, may cause disproportionate increase in serum potassium concentration in sodium-depleted subjects.[23] Marked hyperkalemia is uncommon in patients with hyponatremia in the absence of one of these specific causes.

A specific deficiency of aldosterone may be a cause of hyperkalemia. Patients with congenital adrenal hyperplasia or after adrenalectomy, who secrete little or no aldosterone, may show sodium loss and hyperkalemia when treated with ordinary replacement dosage of cortisone. A curious

syndrome has also been described, in which an unexplained, acquired, rather specific defect of aldosterone led to hyperkalemia and heart block.[57] Treatment with deoxycorticosterone or fludrocortisone has been effective in restoring mineral balance toward normal in these cases.

Drugs Which Interfere with Aldosterone Biosynthesis or Action

Amphenone † is thought to reduce biosynthesis and release of aldosterone and some other adrenal cortical secretions in man.[39] Figure 6 shows a small increase in sodium excretion and fall in potassium output, which accompanied decreased aldosterone output in a patient with the nephrotic syndrome. Related compounds are worth exploring, in an effort to find substances of sufficiently low toxicity to allow further investigation.

Two new synthetic steroids appear to interfere with the action of aldosterone on renal excretion of sodium and potassium.[58,59] Further investigation is in progress to assess the effectiveness and safety of these compounds in patients with hypertension or edema. Figure 7 shows very distinct effects of one of these substances ‡ in releasing sodium and conserving potassium, without any reduction in aldosterone output, in a case of adrenal cortical adenoma secreting aldosterone and other corticoids, with hypertension and evidences of potassium depletion. If such results can be confirmed in other cases, these aldosterone antagonists may fill a real need in investigation and diagnosis, as well as a possible role in therapy.

† The Upjohn Company (Dr. E. W. Young, Medical Division) supplied the amphenone and assisted in this investigation.

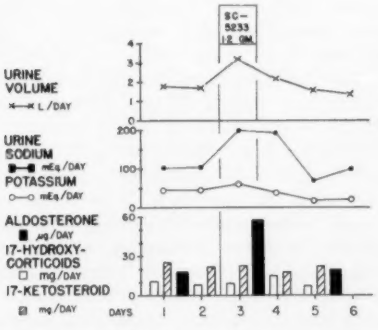

Fig. 7.—Administration of "aldosterone antagonist" (SC-5233) to a patient with adrenal adenoma and syndrome of mineralocorticoid excess. Note increased sodium excretion and reduced potassium loss in spite of rise in aldosterone output.

Concluding Comment

The discovery of aldosterone has opened up new vistas in physiology, functional pathology, and medicine. Investigation has moved at a rapid rate, but speculation has outrun it by far. A great deal of important work remains to be done. Two severe restrictions still limit effective exploration of this field.

First, there is not enough hormone to allow full pharmacologic study in man and for other clinical investigations. Aldosterone is difficult and expensive to extract or synthesize. Present supplies are dependent on the generosity of a few pharmaceutical firms.

Second, the methods for estimation of aldosterone secretion in man are so difficult and laborious that only a few laboratories have undertaken them. Measurement of aldosterone in urine introduces further variables but is feasible in laboratories with the special skills required and with ample personnel, time, and research funds.

The physician with an interesting patient has little chance of finding some one willing and able to measure aldosterone for him on demand. Other studies should be made to determine whether the case is suitable for referral to a special unit with facilities for metabolic studies and aldosterone measurements.

Considerable fundamental information is necessary to interpret the results of aldos-

‡ The synthetic steroid, 3-(3-oxo-17β-hydroxy-4-androsten-17α-yl) propionic acid γ-lactone, Code No. SC-5233, was furnished by the Division of Clinical Research, G. D. Searle & Co., through Dr. I. C. Winter and Dr. C. L. Gantt.

terone estimation. First, because of the variations in methods, the clinician must know what the normal values are by the method which is being used for the determination. Second, he needs to know the diet, the state of hydration, and the electrolyte status of his patient. He will want to know not only whether there is any obvious disturbance of pituitary and adrenocortical function but also the state of the heart, circulation, kidneys, and liver, the level of plasma proteins, hemoglobin, and blood volume, and perhaps even the mental status of certain patients. Since any of these factors may modify aldosterone secretion, it is evident that aldosterone determination is one of the later steps in a thorough medical and metabolic evaluation of the patient. Measurement of this hormone is undertaken only to answer crucial questions.

In spite of these difficulties, a considerable amount of information has been acquired in a brief time. Even the speculation may have served a useful purpose in stimulating further investigations.

There seems little reason to doubt that under appropriate conditions aldosterone excess can lead to edema or hypertension or potassium deficiency. The results of adrenalectomy in man and experimental animals demonstrate that these specific physiological disturbances can be corrected by eliminating the source of excess hormone and that they do not recur when a normal quota of adrenal hormones is suppled. Depression of aldosterone secretion with amphenone has provided a means of assessing the role of the adrenal cortex in edema, but this compound has a variety of undesirable side-effects which make it unsuitable for therapeutic use. The "aldosterone antagonists" currently being tested will be useful physiological tools and may lead to diagnostic and therapeutic applications.

Surgical ablation of adrenal tissue to correct aldosterone excess is obviously justified if adenoma or carcinoma is present and if the patient's condition permits. When bilateral hyperplasia or hypersecretion without anatomic abnormality is present, the indication is less well defined. In hyperplasia leading to a syndrome of potassium depletion and hypertension, subtotal adrenalectomy may be advisable, since prognosis is grave if the situation is allowed to persist. In idiopathic edema, surgery is usually not justified, since the course appears benign and medical treatment usually suffices. In edema secondary to disease of heart, liver, or kidneys, treatment should be directed at the underlying disease which is responsible for adrenal hypersecretion.

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REFERENCES

1. Simpson, S. A.; Tait, J. F., and Bush, I. E.: Secretion of a Salt-Retaining Hormone by the Mammalian Adrenal Cortex, Lancet *2*:226, 1952.

2. Luetscher, J. A., Jr., and Johnson, B. B.: Chromatographic Separation of the Sodium-Retaining Corticoid from the Urine of Children with Nephrosis, Compared with Observations on Normal Children, J. Clin. Invest. 33:276, 1954.

3. Prunty, F. T. G.; McSwiney, R. R.; Mills, I. H., and Smith, M. A.: The Effects of Aldosterone in Addison's Disease and Adrenal Pseudohermaphroditism, Lancet 2:620, 1954.

4. Mach, R. S., and Fabre, J.: Clinical and Metabolic Effects of Aldosterone, in Ciba Foundation Colloquia on Endocrinology: Vol. VIII. The Human Adrenal Cortex, edited by G. E. W. Wolstenholme and Margaret P. Cameron, Boston, Little, Brown & Company, 1955, p. 361.

5. Salassa, R. M.; Mason, H. L.; Mattox, V. R.; Orvis, A. L., and Power, M. H.: Effects of Aldosterone on Water, Electrolyte, and Nitrogen Metabolism in Addison's Disease, Proc. Staff Meet. Mayo Clin. 32:201, 1957.

6. Gaunt, R.; Renzi, A. A., and Chart, J. J.: Aldosterone—a Review, J. Clin. Endocrinol. 15: 621, 1955.

7. Simpson, S. A., and Tait, J. F.: Recent Progress in Methods of Isolation, Chemistry, and Physiology of Aldosterone, in Recent Progress in Hormone Research: The Proceedings of the 1954 Laurentian Hormone Conference, edited by G. Pincus, New York, Academic Press, Inc., 1955, Vol. 11, p. 183.

8. Luetscher, J. A., Jr.: Aldosterone, Advances Int. Med. 8:155, 1956.

9. Simpson, S. A.; Tait, J. F.; Wettstein, A.; Neher, R.; Von Euw, J.; Schindler, O., and Reichstein, T.: Konstitution des Aldosterons, des

neuen Mineralocorticoids, Experientia 10:132, 1954.

10. Axelrad, B. J.; Cates, J. E.; Johnson, B. B., and Luetscher, J. A., Jr.: Aldosterone in Urine of Normal Man and of Patients with Oedema: Its Increased Recovery After Hydrolysis with Acid and with Beta-Glucuronidase, Brit. M. J. 1:196, 1955.

11. Neher, R., and Wettstein, A.: Physicochemical Estimation of Aldosterone in Urine, J. Clin. Invest. 35:800, 1956.

12. Peters, J. P.: Sodium, Water and Edema, J. Mt. Sinai Hosp. 17:159, 1950.

13. Borst, J. G. G.: The Characteristic Renal Excretion Patterns Associated with Excessive or Inadequate Circulation in the Kidney, in Ciba Foundation Symposium on the Kidney, edited by A. A. G. Lewis and G. E. W. Wolstenholme, Boston, Little, Brown & Company, 1954, p. 225.

14. Luetscher, J. A., Jr.: Studies of Aldosterone in Relation to Water and Electrolyte Balance in Man, in Recent Progress in Hormone Research: The Proceedings of the 1955 Laurentian Hormone Conference, edited by G. Pincus, New York, Academic Press, Inc., 1956, Vol. 12, p. 175.

15. Bartter, F. C.: The Role of Aldosterone in Normal Homeostasis and in Certain Disease States, Metabolism 5:369, 1956.

16. Farrell, G. L.; Rosnagle, R. S., and Rauschkolb, E. W.: Increased Aldosterone Secretion in Response to Blood Loss, Circulation Res. 4:606, 1956.

17. Lieberman, A. H., and Luetscher, J. A., Jr.: Stimulation of Adrenocortical Secretions After Air Encephalography, J. Clin. Invest. 36:911, 1957.

18. Rauschkolb, E. W., and Farrell, G. L.: Evidence for Diencephalic Regulation of Aldosterone Secretion, Endocrinology 59:526, 1956.

19. Mulrow, P. J.; Shmagranoff, G. L.; Lieberman, A. H.; Slade, C. I., and Luetscher, J. A., Jr.: Stimulation of Rat Adrenocortical Secretion by a Factor Present in Human Urine and Serum, to be published.

20. Falbriard, A.; Muller, A. F.; Neher, R., and Mach, R. S.: Étude des variations de l'aldostéronurie sous l'effet de surcharges en potassium et de déperditions rénales et extrarénales de sel et d'eau, Schweiz. med. Wchnschr. 85:1218, 1955.

21. Johnson, B. B.; Lieberman, A. H., and Mulrow, P. J.: Aldosterone Excretion in Normal Subjects Depleted of Sodium and Potassium, J. Clin. Invest. 36:757, 1957.

22. Singer, B., and Stack-Dunne, M. P.: The Secretion of Aldosterone and Corticosterone by the Rat Adrenal, J. Endocrinol. 12:130, 1955.

23. Laragh, J. H., and Stoerck, H. C.: A Study of the Mechanism of Secretion of the Sodium-Retaining Hormone (Aldosterone), J. Clin. Invest. 36:383, 1957.

24. Luetscher, J. A., Jr., and Curtis, R. H.: Aldosterone: Observations on the Regulation of Sodium and Potassium Balance, Ann. Int. Med. 43:658, 1955.

25. Llaurado, J. G., and Woodruff, M. F. A.: Postoperative Transient Aldosteronism, Surgery 42:313, 1957.

26. Luetscher, J. A., Jr.; Deming, Q. B., and Johnson, B. B.: Sodium-Retaining Activity of the Corticoid Fraction of Urine of Oedematous Patients, in Ciba Foundation Colloquia on Endocrinology: Vol. IV. Anterior Pituitary Secretion and Hormonal Influences in Water Metabolism, edited by G. E. W. Wolstenholme, New York, The Blakiston Company (division of McGraw-Hill Book Company, Inc.), 1952, p. 530.

27. Luetscher, J. A., Jr.; Neher, R., and Wettstein, A.: Isolation of Crystalline Aldosterone from the Urine of a Nephrotic Patient, Experientia 10:456, 1954.

28. Luetscher, J. A., Jr.; Neher, R., and Wettstein, A.: Isolation of Crystalline Aldosterone from the Urine of Patients with Congestive Heart Failure, Experientia 12:22, 1956.

29. Luetscher, J. A., Jr., and Deming, Q. B.: Treatment of Nephrosis with Cortisone, J. Clin. Invest. 29:1576, 1950.

30. Muller, A. F.; Manning, E. L., and Riondel, A. M.: Étude de l'aldostéronurie chez le sujet normal et chez le cardiaque œdémateux: II. Effet de la prednisone chez les cardiaques, Schweiz. med. Wchnschr. 86:1362, 1956.

31. Vesin, P.; Jacquier, C.; Baulieu, E-E., and Cattan, R.: Hyperaldostéronisme et œdèmes cirrhotiques: Action de la Δ-cortisone, Bull. et mém. Soc. méd. hóp. Paris 73:383, 1957.

32. Barger, A. C.: The Pathogenesis of Sodium Retention in Congestive Heart Failure, Metabolism 5:480, 1956.

33. Davis, J. O.; Howell, D. S., and Hyatt, R. E.: Sodium Excretion in Adrenalectomized Dogs with Chronic Cardiac Failure Produced by Pulmonary Artery Constriction, Fed. Proc. 14:36, 1955.

34. Wolff, H. P.; Koczorek, K. R., and Buchborn, E.: Hyperaldosteronism in Heart Disease, Lancet 2:63, 1957.

35. Muller, A. F.; Riondel, A. M.; Manning, E. L., and Mach, R. S.: Étude de l'aldostéronurie chez le sujet normal et chez le cardiaque œdémateux: I. Effets des variations de l'apport en chlorure de sodium, Schweiz. med. Wchnschr. 86:1335, 1956.

36. Wolff, H. P.; Koczorek, K. R.; Jesch, W., and Buchborn, E.: Untersuchungen über die Aldosteronausscheidung bei Leberkranken, Klin. Wchnschr. 34:366, 1956.

37. Dyrenfurth, I.; Stacey, C. H.; Beck, J. C., and Venning, E. H.: Aldosterone Excretion in Patients with Cirrhosis of the Liver, Metabolism 6:544, 1957.

38. Mach, R. S.; Fabre, J.; Muller, A. F., and Neher, R.: Oedèmes par rétention de chlorure de sodium avec hyperaldostéronurie: Essai de classification des états d'hyperaldostéronisme, Schweiz. med. Wchnschr. 85:1229, 1955.

39. Thorn, G. W.; Ross, E. J.; Crabbé, J., and Van't Hoff, W.: Studies on Aldosterone Secretion in Man, Brit. M. J. 2:955, 1957.

40. Luetscher, J. A., Jr., and Lieberman, A. H.: Idiopathic Edema with Increased Aldosterone Output, Tr. A. Am. Physicians 70:158, 1957.

41. Venning, E. H.; Dyrenfurth, I., and Giroud, C. J. P.: Aldosterone Excretion in Healthy Persons, J. Clin. Endocrinol. 16:1326, 1956.

42. Venning, E. H.; Primrose, T.; Caligaris, L. C. S., and Dyrenfurth, I.: Aldosterone Excretion in Pregnancy, J. Clin. Endocrinol. 17:473, 1957.

43. Landau, R. L.; Bergenstal, D. M.; Lugibihl, K., and Kascht, M. E.: The Metabolic Effects of Progestrone in Man, J. Clin. Endocrinol. 15:1194, 1955.

44. Genest, J.; Koiw, E.; Nowaczynski, W., and Leboeuf, G.: Further Studies on Urinary Aldosterone in Hypertensive Cardiovascular Diseases, Clin. Res. 6:28, 1958.

45. Conn, J. W., and Louis, L. H.: Primary Aldosteronism, a New Clinical Entity, Ann. Int. Med. 44:1, 1956.

46. Milne, M. D.; Muehrcke, R. C., and Aird, I.: Primary Aldosteronism, Quart. J. Med. 26:317, 1957.

47. Eales, L., and Linder, G. C.: Primary Aldosteronism: Some Observations on a Case in a Cape Coloured Woman, Quart. J. Med. 25:539, 1956.

48. Garrod, O.; Simpson, S. A., and Tait, J. F.: Aldosterone, Lancet 1:860, 1956.

49. Mader, I. J., and Iseri, L. T.: Spontaneous Hypopotassemia, Hypomagnesemia, Alkalosis and Tetany Due to Hypersecretion of Corticosterone-like Mineralocorticoid, Am. J. Med. 19:976, 1955.

50. Lieberman, A. H.; Slade, C. I.; Krück, F., and Luetscher, J. A., Jr.: Secretion of Corticosteroids Other Than Aldosterone in Conn's Syndrome, Clin. Res. 6:93, 1958.

51. Foye, L. V., Jr., and Feichtmeir, T. V.: Adrenal Cortical Carcinoma Producing Solely Mineralocorticoid Effect, Am. J. Med. 19:966, 1955.

52. van Buchem, F. S. P.; Doorenbos, H., and Elings, H. S.: Primary Aldosteronism Due to Adrenocortical Hyperplasia, Lancet 2:335, 1956.

53. Luetscher, J. A., Jr., and Axelrad, B. J.: Sodium-Retaining Corticoid in the Urine of Normal Children and Adults and of Patients with Hypoadrenalism or Hypopituitarism, J. Clin. Endocrinol. 14:1086, 1954.

54. Haydar, N. A.; St. Marc, J. R.; Reddy, W. J.; Laidlaw, J. C., and Thorn, G. W.: Adrenocortical Insufficiency with Normal Basal Levels of Urinary 17-Hydroxycorticoids: Diagnostic Implications, J. Clin. Endocrinol. 18:121, 1958.

55. Prader, A.; Spahr, A., and Neher, R.: Erhöhte Aldosteronausscheidung beim kongenitalen adrenogenitalen Syndrom: Ein Beitrag zur Pathogenese des Syndroms, Schweiz. med. Wchnschr. 85:1085, 1955.

56. Schwartz, W. B.; Bennett, W.; Curelop, S., and Bartter, F. C.: A Syndrome of Renal Sodium Loss and Hyponatremia Probably Resulting from Inappropriate Secretion of Anti-Diuretic Hormone, Am. J. Med. 23:529, 1957.

57. Hudson, J. B.; Chobanian, A. V., and Relman, A. S.: Hypoaldosteronism: A Clinical Study of a Patient with an Isolated Adrenal Mineralocorticoid Deficiency, Resulting in Hyperkaliemia and Stokes-Adams Attacks, New England J. Med. 257:529, 1957.

58. Kagawa, C. M.; Cella, J. A., and Van Arman, C. G.: Action of New Steroids in Blocking Effects of Aldosterone and Deoxycorticosterone on Salt, Science 126:1015, 1957.

59. Liddle, G. W.: Sodium Diuresis Induced by Steroidal Antagonists of Aldosterone, Science 126: 1016, 1957.

Books

Edited by William B. Bean, M.D.*

The Quicksilver Doctor. By Kenneth Dewhurst. Price, 1 guinea (about $3). Pp. 192, with illustrations. John Wright & Sons, Ltd., 42-44, Triangle West, Bristol 8, England. 1957.

Ever since I read William Osler's essay about "Thomas Dover, Physician and Buccaneer," I have been fascinated with the thought that at least one physician was a real pirate. Many have been accused, but few, chosen. Dewhurst emphasizes an important distinction I was not fully aware of between a buccaneer and a privateer. The buccaneer or pirate took as his prize any ship or person, being outside the law, without commission and without regard for nationality. The privateer operated under commission of his country as an agent against the shipping of his country's enemies. Dewhurst also tells us that the word buccaneer was derived from the word *boucan*, a process of jerking meat over a smoky fire practiced by the natives of the Caribbees. His book is packed with all kinds of miscellaneous information, giving, by the bye, a really excellent view of the the deplorable condition of medicine at the time Dover flourished. Professional uneasiness, rampant quackery, and harsh jealousy among medical men were in gorgeous bloom in a day when orthodox medicine almost always failed to cure or even alleviate the common diseases. Medical practice was based on one of the great forgotten contributions of "medicine" to the survival of the fittest. It frequently conspired to make a mild disorder fatal and a fatal disorder more speedily fatal than was its nature.

Dover is still remembered in Britain and on the continent as the inventor of Dover's powders used to induce sleep and a gentle sweat and to cure many a self-limited trouble. Even in his day of unusual people he was a wild and original character. For those who get pleasure from a racy narrative, the story tells of the capture of Guayaquil, the battles on the high seas—these doings I find delightfully and emphatically piratical and not privateerical. There were engagements at sea and circumnavigation of the globe under the most primitive conditions with Dover as physician and part-time commander of the expedition. The rescue of Alexander Selkirk and all the to-do about the Robinson Crusoe tradition are set forth against the background of turbulent, brawling, gusty, lusty England some two hundred fifty years ago. Finally, the motley crew and interesting leaders of this wonderful voyage returned to England. After long and vexatious litigation, long and litigious vexations, the spoils were distributed. Dover emerged a wealthy man. But his great wealth, accumulated on the high seas, was dissipated in the extravagantly futile investments of the South Sea Bubble, which came crashing to the ground in the same sort of sickening shock which some of us remember at least hearing about in the stock market crash of 1929. Dover was forced to return to practice, where he achieved a name and fame for his contentious nature, his pompous and irascible conceit, and his conduct of medical practice based on the exhibition of quicksilver for any and all complaints. His bland faith in this as panacea led to his nickname "the quicksilver doctor."

He published a book, "The Ancient Physician's Legacy," a potpourri of nostrums, cures, household remedies, and brief descriptions of disease. It was a pot-boiler, an advertising scheme to promote his practice. It did. It had remarkable sales and quickly ran through several editions, including some pirated by competitors who could not outwit him and therefore used his book. In addition to his use of quicksilver, Thomas Dover's "Legacy" was forward-looking in its praise of inoculation for smallpox and popularization of cold bathing, a true heresy in an unwashed age. Although Dover bled excessively, he did not bleed indiscriminately for all fevers.

The state of medical criticism of the time is skillfully portrayed by Dewhurst. Among the pamphlets "reviewing" Dover's "Ancient Physician's Legacy" was Daniel Turner's "The Ancient Physician's Legacy Impartially Survey'd"; a pamphlet by the "Mercurialist," called

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"A Short Review of the Quicksilver Controversy"; another, on "The Use and Abuse of Mercury," by a "Country Physician," with the rebuttal called "Remarks upon a Late Scurilous Pamphlet, a 'Review of the Quicksilver Controversy,'" in which Dr. Turner's character as a "Great and Impartial Historian in Regard to the Same is granted and the Authors own Impartiality, Sincerity, Falsehood, and Gross Ignorance are Set Forth." Another interesting and intemperate attack was H. Bradley's "Physical and Philosophical Remarks on Dr. Dover's Late Pamphlet." This book about Dover gives a detailed analysis of all these pamphlets and broadsides with their nasty attacks based on hostility or envy. They illustrate the deplorable depth to which criticism had sunk and the low state of medicine of the times. But we, with a sweeter temperment in a cooler time, must remember that bile is bitter, and black bile, melancholy, is one of our four natural humors.

WILLIAM B. BEAN, M.D.

Bilateral Polycystic Disease of the Kidneys: A Follow-Up of Two Hundred and Eighty-Four Patients and Their Families. By O. Z. Dalgaard, M.D. Translated by Harry Cowan, B.Sc. Price, not given. Pp. 255, with 37 figures. Ejnar Munksgaards Forlag, Nørregade 6, Copenhagen, 1957.

The physician usually looks at bilateral polycystic disease of the kidneys as an inherited condition characterized by enlarged kidneys, uremia, and a gloomy prognosis and lets it go at that. Dalgaard has made a painstaking analysis of three hundred fifty patients with bilateral polycystic disease of the kidneys, which amply fulfills his stated aim of adding to our knowledge of the heredity and the clinical aspects of this condition.

The author began his study by attempting to ascertain *all* the cases of bilateral polycystic kidneys that appeared in Greater Copenhagen from 1920 to 1953, inclusive. He examined the card indexes and annual statistics of the medical and surgical departments of the Copenhagen hospitals, the autopsy records of the hospitals (143 propositi were culled from 98,000 autopsy records), the card indices of the radiology departments of the hospitals (he examined all available x-rays of kidneys said to contain cysts of any type), the records of a private clinic with an interest in the surgical treatment of polycystic renal disease, and the card indices of the Institute of Human Genetics of Copenhagen University. From these sources he ascertained 242 propositi. By first-hand contact with available relatives he found another one hundred eight persons in whom the diagnosis could be established. He examined autopsy records and clinical records of all deceased patients and personally examined all but a handful of the living patients. He obtained information in a total of 1634 close relatives of the propositi, adequate to make the diagnosis of polycystic disease unlikely. I believe that the author came as close as is humanly possible to finding all the cases of this condition within the time and geographical limits he set up. The author's criteria for diagnosis were firm, and the data, well presented. His conclusions regarding the genetic aspects of the condition, therefore, seem valid. It comes as a shock to realize that in the past we have blithely accepted the hereditary nature of bilateral polycystic kidneys on most inadequate grounds. The present monograph for the first time corrects this deficiency. An interesting commentary on the inadequacies of many clinical observations is the fact that Dalgaard noted that the clinical histories of only 15 of the 242 propositi recorded other members of their families as having polycystic kidneys and that some kind of kidney disease was noted among the families of only another 26 of the propositi, and yet Dalgaard found polycystic kidneys in the families of 162 of 232 propositi (he was unable to perform genealogic studies in the case of 10 of the propositi).

In addition to the genetic analyses, the data contained in this monograph are presented in such a way that the reader obtains a valuable, excellent, and well-documented grasp of the diagnosis, natural history, and prognosis of bilateral polycystic renal disease. It is recommended not only as the most definitive treatise available on this condition but also as a model for a careful and thorough study of a disease to which not many physicians are inclined to devote much thought.

DAVID P. EARLE, M.D.

Diabetes Mellitus, with Emphasis on Children and Young Adults. By T. S. Danowski, B.A., M.D. Price, $13.50. Pp. 510, with numerous illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1957.

This book is noteworthy for its comprehensiveness. The first of three sections is devoted to the metabolism of carbohydrate, protein, and fat and to the interplay of the influences of

the endocrine glands in both the normal state and diabetes. The second and third sections deal with clinical aspects—first, the routine problems of management of diabetes, and second, its complications. Appropriate discussions of related topics, such as electrolyte balance, pregnancy, growth, personality, and emotional factors, are included. The illustrations are relatively simple charts, tables, and diagrams, which do much to enhance the text.

The author has successfully presented much experimental work and clinical observation to explain present-day concepts. The successive bits of evidence thus derived are nicely combined without falling into a "Book of Genesis" style, which this type of presentation fits so easily. The subjects of diabetes and metabolism contain many controversial or poorly understood points. These are fully considered, and the author usually states his opinion, which gives continuity and a chance for disagreement to those so inclined.

This book is not so much to be read as to be studied, for it contains much correlated information. It will serve well both for the primary acquisition of knowledge and as a reference. The very extensive bibliography accompanying each chapter adds to its value for the latter purpose.

ROBERT C. HARDIN, M.D.

Adventures in Medical Education. By G. Canby Robinson, M.D. Price, $5. Pp. 338, with illustrations. Harvard University Press, Cambridge 38, Mass., 1957.

Each age, period, and place has a tendency to look upon itself as the greatest, and this is better than to have an inferiority complex or mock humility. It is the unusual person who can escape from his own preoccupations and experiences to produce valid generalizations. People fifty years ago, a hundred years ago, or at any other bygone time often wrote as though they lived in the best, most exciting, or most advanced age. Any time can claim to be current and contemporary, but history compares at leisure. The story of repeated alterations in medical customs, philosophies, and practice, what is so often called cheerfully "modern advances," make it very difficult for any age to judge itself. Canby Robinson's "Adventures in Medical Education" leads us through his early days at the brand new Johns Hopkins, his later hospital training, and his residency; the exciting developments of the Rockefeller Institute and Rockefeller Hospital; the regeneration of Washington University School of Medicine, in St. Louis, under the far-sighted and effectual stimulus of Robert Brookings; the rejuvenation and consolidation of Vanderbilt University School of Medicine, and the struggles to launch the modern machinery of that vast medical city, the New York Hospital-Cornell Medical College, and keep it afloat during the retrenching years of the depression. In each of these Robinson had intimate, important, and sometimes commanding functions, which are detailed factually but without modesty, false or not. Then there was a brief stay at Peiping Union Medical College. These events and experiences seem to be merely previews of Robinson's growing emphasis on the social aspect of medicine, which he was able to practice at first-hand only after he had been relieved of his responsibilities at Cornell.

Robinson was one of the pioneers in what we now call psychosomatic medicine in its formal sense. He was the first full-time Professor of Medicine devoting his whole attention to the relationship of social, emotional, economic, and other environmental factors in the precipitation or aggravation of disease and the many related aspects of treatment, convalescence, and rehabilitation. One might look upon the entire story Robinson gives of his peripatetic career in developing a number of medical schools along modern principles of medical education as a fitting sequel to Abraham Flexner's report. It is the story of the rise of modern American medical education and its keystone, full-time teaching in a university setting. One gets a clear view of the usually overlooked contributions of the Middle West to Johns Hopkins, notably Billings, from Cincinnati, who as advisor made large contributions to the concept and fulfillment of the hospital-medical school complex, and the behind-the-scenes operations of Mall, who was a major factor in determining policies which Welch so skillfully put into effect. It is unusual for writers these days to be so perceptive as to recognize Daniel Drake and the early origins of medicine in the Middle West. Here it reached a high level of perfection at a time when it still was floundering at Harvard and many of the Eastern schools, which came up with the great rise in medicine following the development of The Johns Hopkins Medical School. Likewise the contributions of Michigan to The Johns Hopkins is clearly delineated.

Occasionally Robinson seems to be carried away with his enthusiasm for those places which he knows well. Despite the brilliance of the faculty and the great accomplishments of Washington University, it is difficult to believe that the appointment of Dock, Opie, Howland, Erlanger, Shaffer, and Terry was "undoubtedly the most remarkable accomplishment in the history of American medical education," though none will deny it was an effective and fruitful combination.

One learns from this book, as he can nowhere else so clearly, the fact that America has been much wiser in lavishing her largess on medical expenditures in foreign lands than in other ways. Who can think of a development comparable to the oases of Western Medicine in China, made possible by men and money from the United States. Despite the turn of political events, this influence remains and flourishes.

One of the great risks as well as charms of autobiography is the emphasis upon the story teller at the expense of the story. Robinson avoids this, but he does not escape the provincial, nay, the parochial, value judgment, the implication that where he is or has been is a great place, and the veiled corollary that others need less attention. I had the uneasy feeling that Washington University Medical School, at St. Louis, was bounded on the East by Johns Hopkins and the Rockefeller Institute, on the West by Peiping Union Medical School, and on the Southeast by Vanderbilt. But it is a virtue of autobiography that it is not history. These tales of Robinson's adventures in medical education, covering the rise and flowering of full-time medicine in the United States in a space of fifty revolutionary years, will be a valuable source book for future historians.

WILLIAM B. BEAN, M.D.

Systemic Arterial Embolism: Pathogenesis and Prophylaxis. By John Martin Askey. Price, $5.75. Pp. 157, with 45 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1957.

My anticipation, based on a high regard for Dr. Askey's writings, perhaps set my hopes too high for this monograph. The first third of the book details clinical situations favoring endocardial thrombosis. The information is well presented but well known. The middle third delves into certain aspects of coagulation and embolism, but the delving is not deep enough. The last third discusses treatment, emphasizing mitral valvulotomy and anticoagulation. The latter is discussed with more enthusiasm and less skepticism than my bias would prefer. In this section, particularly, studies from various sources are not critically weighed.

Systemic Arterial Embolism is better than the average clinical monograph. It is clearly organized, well written, and easily read. My expectations, and not the book, may account for my failure to vibrate to it. Others may not be similarly handicapped.

ANDREW KERR JR., M.D.

Clinical Gastroenterology. By Eddy D. Palmer. Price, $18.50. Pp. 630, with 216 illustrations. Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 49 E. 33d St., New York 16, 1957.

Superbly delightful medical reading is Palmer's "Clinical Gastroenterology." Its untraditional approach to diseases of the intestine and juxtaposed organs has already incited controversy. I take a firm stand with the concepts expressed and the scholarly approach exemplified by this book. A questioning attitude, checked at the bedside and in the laboratory, commands attention for each unit. To one who is not primarily a gastroenterologist, Palmer's approach to these problems is refreshing.

The general internist will find much in the book that agrees with his daily experiences on the ward and in the office. In this book, gastroenterology is pushed in the turbulent stream of modern medicine. With Palmer's help, the subspecialty swims well, heading upstream, eyes open, efficiently taking in pure air before plunging deeply. The modern outlook reflected in this book is not in documenting efforts to make gastroenterology an exact clinical science. Dull studies are not detailed here. Its modern outlook comes from looking at the patient first and his symptoms next. Resisting, on one hand, the slide-rule viewpoint of research investigation and, on the other, the free-floating delight of psychosomatic interpretation, Palmer's approach remains that of a doctor concerned with the patient.

It is difficult to highlight sections of the book. The sections on peptic ulcer, gastric carcinoma, irritable colon, and amoebiasis are particularly appealing. The introductory paragraphs of each section exemplify the pleasant restrained scholarly touch. Throughout, words are carefully chosen and well used and convey clearly to the reader the meanings intended.

It is picayune to note minor errors in this book. The paragraphs on mushroom poisoning contain error. The statement about right atrial enlargement causing a shift of the barium-filled esophagus is probably not correct. The word serendipitous, often used, is misspelled. The sentence, "There is no sex preference," is used several times. "Chyme and chyle wait for no man" strains the pun too much.

The book reflects good publishing craftmanship. The two-column page is easy to read. Some of the drawings add very little. The index is adequate.

The book is highly recommended for student and resident reading. The general practitioner and general internist will find it of much help in clarifying their handling of routine patients.

ANDREW KERR JR., M.D.

For Future Doctors. By Alan Gregg, M.D. Price, $3.50. Pp. 165. The University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1957.

The death of Alan Gregg last year removed from the scene one of the great medical educators and physicians of our time. This statement no doubt seems extravagant, since Alan Gregg was never a professor in a medical school; beyond his internship and residency he was not a practicing physician. Nonetheless, without academic connection or experience in practice, his influence has pervaded and improved medical education and medical practice in this country. He worked as a member of the Rockefeller Foundation. To a large degree the considerable achievements of the Rockefeller Foundation in medical education are a reflexion of the wisdom and leadership of Alan Gregg. He came to be looked upon as a medical wise man who could suggest proper therapy for a medical school which was undergoing dry rot or could calm feuds among the various dynasties of the splintered specialties of a particular medical college. Much of his work as an elder statesman was behind the scenes, suggesting, a hint here, a sharp question there. Unobtrusively he helped to obtain the proper jobs for the proper people at the right places. Not only did Alan Gregg have wisdom and courage, but he had great insight. His ability to express himself in salty and delightful terms is revealed in his books and numerous essays and addresses. Anyone interested in American medicine will be pleased that the wit and wisdom of these fugitive papers, ephemeral commencement addresses, and forgotten lectures are collected in this book, for the present illumination of future doctors as well as the future improvement of present doctors.

One of my great pleasures was the exchange of letters and reprints with Alan Gregg during the last ten years or so of his life. He knew of many of my interests, and I knew some of his. From time to time he would send me out-of-the-way references or apposite comments or bits of lore he had picked up on his travels or from recent experience. I learned that he could stimulate by praising and could provoke me to all-out performance by the most casual aside, a mere hint which became a challenge. Even in his flattery, which at times was lavish, he had the curious capacity to stimulate one in the direction of higher achievement. When one is tired of hearing snide defamation of character or undercutting of somebody's work, complaint devoid of critique, and criticism reduced to the level of gossip, it is a joy to receive a letter with hearty and heady comments. Naturally, I treasure his letters, but even more, the memory of his luminous presence and his delightful wit. Those who were not fortunate enough to know him can get a good look at the kind of man he was from reading the sparkling, delightful, and yet serious and extremely thoughtful essays contained in this book "For Future Doctors" which The University of Chicago Press has printed, adding luster at once to itself and to Alan Gregg's memory.

WILLIAM B. BEAN, M.D.

Pediatric Cardiology. By Alexander S. Nadas. Price, $12. Pp. 587, with 343 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

"Pediatric Cardiology" is an eminently readable account of the personal experiences of a mature leader in this field. The one real objection is related to the title of the book. It implies official recognition of a new specialty; it implies approval of further and farther cleavage in medicine, and it implies the issuance of an authoritative text. I hope that none of these implications have entered Dr. Nadas' mind, and, indeed, if the book had been entitled "pediatric aspects of cardiology," all would have been well, because this is what the book

emphasizes. The volume is a welcome and often delightful supplement to anyone concerned with the clinical and laboratory aspects of heart disease. For him the text offers much that is useful and informative. For the pediatrician who desires to learn cardiology, the text should prove less serviceable, since many important aspects of general cardiology had to be treated lightly. The graphic registration which forms the basis for many illustrations is of less than optimal quality, and many useful techniques, such as left heart catheterization, the analysis of the central arterial pulse, direct oximetry, and differential dye analysis, are entirely omitted. There are some who consider the omission of differential dye oximetry during a right heart catheterization in congenital cardiac disease a punishable crime. The author may be less interested in such technical matters, but the ambitious title does require a somewhat broader and more careful coverage of these aspects. By and large, however, these are minor objections.

Clinical cardiology now requires a full integration of the observation obtained by "physical" diagnosis (a curious misnomer) with various and often difficult laboratory procedures, much as modern hematology relies heavily on blood smear, biochemistry, and hematocrit tubes. Dr. Nadas provides this integration on almost every page and yet manages to retain the charm of a personal narrative based on a wealth of often unusual case material. This is an accomplishment which is notably lacking in many of the modern texts of cardiology and internal medicine. Thus, the book is welcome.

HANS H. HECHT, M.D.

The Electrophysiology of the Heart. Hans H. Hecht, Consulting Editor. Price, not given. Pp. 493, with 274 illustrations. The New York Academy of Sciences, 2 E. 63d St., New York 21, 1957.

This volume, published as Article 6 of Volume 65 of the Annals of the New York Academy of Sciences, is the result of a conference organized by Dr. Hecht and held at the Academy in February, 1956. It contains the text of the papers presented at the conference, as well as the discussion following them, augmented and brought up to date where necessary and provided with an extensive bibliography. Forty-four of the most distinguished physiologists and clinicians from all over the world contributed original papers, and a score more participated in the discussions and round-table conferences. The result is a lasting recapitulation and summary of our present-day knowledge concerning the electrical events in the heart which are responsible for the electrocardiogram and a fitting monument to Dr. Frank N. Wilson, who first applied the principles of biophysics and mathematics to the interpretation of clinical electrocardiograms and to whom the conference was dedicated. Dr. Hecht has done an outstanding job of editing in arranging the separate presentations in a logical and readable sequence and has filled in any gaps in the continuity of thought which may have been left by the separate speakers.

The book is divided into five parts: 1. the cellular events during the cardiac cycle; 2. spread of the impulse through cardiac muscle; 3. cardiac recovery; 4. distribution of electric potentials in volume conductors, and 5. analysis of the surface electrocardiogram. Part 1 will give the clinician insight into the biochemical and metabolic processes which are the basis of the electrocardiogram. Part 2 will help him interpret the QRS complex and the conduction disturbances and also contains a most advanced and clinically significant discussion on the nature of anomalous ventricular excitation or the Wolff-Parkinson-White syndrome. Chapter 3 discusses the nature and significance of the T and U waves and the ventricular gradient, while Parts 4 and 5 discuss the vectorcardiogram as well as electrocardiographic changes due to extracardiac factors, such as the peculiarities of leads and conductivity of the tissues surrounding the heart. The book will be very useful to every clinician who wants to gain a deeper understanding of the electrocardiogram and cardiac irregularities and indispensable to all those who want to contribute, themselves, to the development of these fields of interest.

E. LEPESCHKIN, M.D.

Chemistry of the Lipides as Related to Atherosclerosis. By Irvine H. Page, M.D. Price, $8.50. Pp. 342. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

To most physicians atherosclerosis is a disease enshrouded in mystery. They are puzzled by the confused state of knowledge regarding basic causes and treatment. However, it is clear that atherosclerosis appears to be a disorder of lipid metabolism. The past ten years have seen a great surge of interest and work in lipid metabolism. A large amount of in-

formation, shedding light but not certainty on some aspects of atherosclerosis, has been accumulated. Most of this information is scattered so diffusely and in such quantity throughout the medical literature that one person can no longer gather in this wealth of knowledge. Nor is he in a position to interpret the specialized chemical and physiological details. There is a need for periodic publications which will bring together in one volume the most important basic science contributions in this field.

In May, 1957, a symposium was sponsored by the National Advisory Heart Council to deal with the "Chemistry of Lipids as Related to Atherosclerosis." Ninety-five scientists participated in providing a much-needed synthesis of knowledge. This book of the same title and edited by Irving Page resulted from their discussions. It offers eighteen separate essays, each by a recognized authority, on various phases of lipid metabolism, ranging from the digestion and absorption of fats, their transport and deposition, to their synthesis and oxidation. The lipoproteins and the clearing-factor enzyme, lipoprotein lipase, are covered thoroughly. The phospholipids, the sphingolipids, the unsaturated fatty acids, and the nonesterified fatty acids are topics of individual discussion. One essay deals with the control of serum lipid levels exerted by the various dietary fats. Of great value is the discussion which follows each presentation. Here all ninety-five of the participants in this symposium have an opportunity to offer comments or points of disagreement based upon their own individual experiences. Finally, the bibliography of each discussion is complete and up to date.

This book can be recommended to physicians, chemists, physiologists, and nutritionists. The editor, the participants, the National Advisory Heart Council, and the publisher are to be congratulated on their splendid effort.

WILLIAM E. CONNOR, M.D.

The Incurable Wound. By Berton Roueché. Price, $3.50. Pp. 177. Little, Brown & Company, 34 Beacon St., Boston 6, 1957.

Today's murder mystery may have a physician as amateur detective. Even more unpleasant is the situation that the physician too often is suspected of the crime. Indeed, he may even be guilty of it. Thus the role of the physician in society is reflected in the dim view taken of him and his activities by the average writer of modern detective stories. I have often wondered why so many exciting medical mysteries have been given so little publicity and have so rarely been seized upon as the theme for novels, short stories, or even popular mystery writing. It would appear now that this deficiency is on the way to being corrected. Perhaps Berton Roueché single-handed may fill this deficiency and even lead others to his own now unique distinction in using scientific and medical themes in well-written and exciting stories full of mystery and suspense. In an earlier book, "Eleven Blue Men," he cracked this neglected front. The stories in "The Incurable Wound" all appear originally in *The New Yorker*. Some are presented as simple narratives; some, as interesting reports, and others, more or less as mysteries. A victim of amnesia is described with sympathy and accuracy in one tale. Rabies and its newly recognized host in this country, the bat, is described in a way resembling the more macabre tales of Edgar Allen Poe, though without the same final and fatalistic horror. Occupational and domestic poisons, some in the forms of simple medicines of which our society seems to make five new ones for every one it discards, are presented graphically. Roueché describes the unhappy poisoning of children by careless parents or by the children's exploring propensities and the accessibility of candy-covered pills, samples in the physicians' mail. The strange distortions of personality occurring in someone going off the track under the influence of steroids is presented graphically with insight and with great artistry. The physician who likes his murder mysteries cleaned up a bit and who enjoys reading excellently written documentary tales of medicine full of fascination and curiosity will find "The Incurable Wound" a splendid antidote for so much that is hostile to the physicians—the outbreak of antimedicine and antiscience in the contemporary press. One annoying cliché in all the stories was the author's self-conscious seeking for the anonymity of his subjects which he explained in an already self-evident way by saying "I'll call him so-and-so." This is an inconsequential blemish. I do not even know why it annoyed me. It should not detract from the stories which reveal a writer able to whet popular interest in the incomparable manner of the early de Kruif.

WILLIAM B. BEAN, M.D.

Peripheral Vascular Disease. By A. J. Barnett and J. R. E. Fraser. Price, $9.50. Pp. 219, with illustrations. Cambridge University Press, 32 E. 57th St., New York 22, 1955.

It is difficult to put out any new and useful information about peripheral vascular disease unavailable to practitioners in this country from the standard textbooks of Allen, Hines, and Barker; Wright; Abrahamson; and the British treatise on the same subject by Martin, Lynn, Dible, and Aird. This book by Barnett and Fraser is based on the Stawell Memorial Prize of the British Medical Association (Victorian Branch for the year 1952). It is a sound general discussion of peripheral vascular disease. The historical review includes a good many items not often found in such books: a longer discussion of the physiology of blood vessels and a detailed investigation of the methods of diagnosis of arterial insufficiency and of the pathology of peripheral vascular disease. The main and longest chapter describes the clinical features of peripheral vascular disease and is followed by a short essay on treatment. Thus it follows the orthodox textbook style and is a satisfactory presentation of the problem. The illustrations are not outstanding, though there are enough line drawings to supplement the photographs. This book will appeal more to the undergraduate student and beginner than to someone who has had much experience in peripheral vascular disease. It is not nearly as complete or detailed as the texts already available. The price seems high.

WILLIAM B. BEAN, M.D.

Health and Medical Care in New York City: A Report by the Committee for the Special Research Project in the Health Insurance Plan of Greater New York. Price, $7.50. Pp. 275. Commonwealth Fund, Harvard University Press, Cambridge 38, Mass., 1957.

This volume is the first report of a questionnaire survey on medical care, including preventive medicine, begun in 1952 under the surveillance of a special study group of the Health Insurance Plan of Greater New York (H. I. P.). The book contains thirteen chapters and eight appendices which together form a wealth of information on prepaid medical care. Chapters cover the following items among others: objectives and methods of the household survey; insurance status of household members; physician contacts, 1951; persons and families with family physicians; pediatric services; morbidity, disability and medical care related to specific illness conditions; hospital expenses, 1951; attended dental conditions, and preventive health services. The appendices relate to survey methodology and sampling design, with a record of detailed statistical tables on file.

The undertaking of H. I. P. in 1947 was a pioneering venture of the first magnitude in a relatively uncharted field. Much money has gone into this study, and this book describes the preliminary findings of medical care experience of enrollees of H. I. P. and compares this with the experience of families in New York City who were nonenrolees in the plan. It is doubtful that the comparison answers the posed questions satisfactorily.

The book appears to be candidly written, and the authors realize that medical care is fluid and that this is at least the story of one "beginning" in the field. The preface and foreword do much to present the inherent problems associated with a medical-care undertaking of this kind, and Parran states in the foreword, "As might have been expected, the present study raises almost as many questions as it answers." Supplementary reports are proposed. The material presented in this volume is of great value to persons interested in medical care and to those concerned with developing a medical care program.

FRANKLIN TOP, M.D.

Endocrine Pathology of the Ovary. By John McLean Morris, M.D., and Robert E. Scully, M.D. Price, $8.50. Pp. 151, with 75 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1958.

This small volume is unique in that it presents an up-to-date endocrine interpretation of ovarian pathology. The authors are cognizant of the ambisexual nature of the origin of some tumors and also of the ambisexual action of some of the steroid hormones. Their discussion of the non-neoplastic abnormalities, such as hyperthecosis and stromal hyperplasia, is of special interest.

The text is well written and well organized. The illustrations are excellent. Each chapter is documented by a well-chosen bibliography.

JAMES T. BRADBURY, Sc.D.

The Springs of Virginia. Third edition. By Perceval Reniers. Price, not given. Pp. 301, with illustrations. University of North Carolina Press, Chapel Hill, N. C., 1955.

To those who have had the good fortune to visit Hot Springs or the White Sulphur Springs in the Virginias it will be no great surprise that these outstanding resorts are all that remains of a flourishing culture which reached a peak perhaps a hundred years ago and dwindled after the Civil War. Probably the Civil War was only a minor factor in the decline and decay of the Virginia spas. Some people today believe that the spring resorts of the mountains will come back into their own when the current cult of sunburned nudity at the beach dies out, as all cults have a way of doing. There seems to be no evidence that this trend is weakening notably at the moment. But as James Baker and others have pointed out so skillfully, the main reason for the flourishing of the springs at a time when Virginia included what is now West Virginia was the numerous epidemics which plagued the South and gave a healthy reason for escaping seaboard cities and those along the Mississippi. Perhaps equally weighty was the need to get away from a hot humid environment to the cool of the mountains. But even beyond this we have the still strong forces of snobbishness, of keeping up with the Joneses, and a marriage market among the elite which had developed to a high level of efficiency during the heyday of the 1850's.

In addition to these forces, there were others pro or con, such as the general economic situation, the price of tobacco and cotton, and the coming and going of panics and of boom times. Perceval Reniers has given a delightful story of the "curing" and mating, the one for the older, the other for younger generations, which went on furiously side by side for well over a century. In this charming book you will find legends of many a cure in the strange life of the spas whose waters were impregnated with minerals, heat, and fashion. Here are spread before us the glamor girls of their day, the Southerner and his ladies on parade during the last flowering of chivalry in the old South, the food, the gambling, the dances, costumes, the music, the tremendous crowding during the peak season of popularity. Here in peacock alley we have the social peak order in the social hierarchy of the long lost South. Social prestige rather than any therapeutic virtue of the fetid and foul-smelling waters determined the popularity of any particular spa. The medical effects of this whole program were never closely evaluated. The function as a social safety valve and marriage mart fulfilled a valuable function well.

WILLIAM B. BEAN, M.D.

The Respiratory Muscles and the Mechanics of Breathing. By E. J. Moran Campbell, M.D., Ph.D., B.Sc.(Lond.), M.R.C.P.(Lond.). Price, $4.25. Pp. 128, with 32 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1958.

This is a thorough description of the performance of the muscles used in breathing. Included are history of previous concepts of the role played by various muscle groups, the anatomy and mechanical actions of respiratory structures, and electromyographic data obtained during respiration. These are correlated by the author to present a concept of the mechanics of breathing. The muscle groups so studied include those of the thorax, neck, back, abdomen, and larynx. They are studied both in quiet respiration and in varying degrees of hyperventilation. Most studies were done on normal patients, but some data are included on emphysematous subjects. A brief discussion of control and coordination of respiratory muscles and the work of breathing is included. There is also a discussion of the pressure-volume diagram of the thorax.

The material is presented in a concise manner and in terminology which is readily understood. Graphs and actual recordings are used to clarify the presentation. This report is one of physiology and not of clinical disturbances in respiration. It is a complete collection of the currently available information on this subject. A large bibliography and an appendix describing techniques and methodology is included in the book.

WILLIAM B. HAMILTON

Clinical Gastroenterology. By Eddy D. Palmer, M.D., F.A.C.P. Price, $18.50. Pp. 630, with 216 illustrations. Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 49 E. 33d St., New York 16, 1957.

Dr. Palmer has written a book whose subject matter is precisely what the title indicates, namely, clinical gastroenterology. As he states in the preface, experimental gastroenterology is not discussed and emphasis has been placed "on those subjects which seem to have special meaning for gastroenterology as it is practiced during the present era." This

book tells the story of clinical gastroenterology as it is seen and practiced by the author. It fills a definite need in the present-day literature and should be a valuable aid to all practitioners of medicine except those working in narrow subspecialties.

Most phases of gastroenterology are well covered, with the exception of the liver. There is a brief discussion of jaundice, and the section on liver-function tests is sketchy. The part on the esophagus is well done, as would be expected in view of Dr. Palmer's well-known interest in that portion of the gastrointestinal tract. In the discussion of cardiospasm, the methacholine (Mecholyl) test is mentioned, but no directions are given for its performance, its value is not debated, nor is the previous work on the subject referred to in the bibliography. It is strange that such useful information is omitted in a volume intended primarily for the practitioner.

Nearly all the discussions on therapy are of a good common-sense variety, and many helpful hints are included. This is especially true of the sections on the treatment of hepatitis and of chronic ulcerative colitis.

Dr. Palmer writes in a very readable and even entertaining style. It is in sharp contrast to much of the stilted grammar and sentence construction of present-day medical literature. I find this a delightful change. There are many "informal" descriptive phrases scattered throughout the book. For instance, in discussing the personality of persons with chronic nonspecific proctitis, the author states "momism is not found. Some patients seem to be calculators and big dealers." Included in the book are good discussions of some of the uncommon conditions in gastroenterology, such as proctalgia fugax and hysterical nongaseous abdominal distention. In the preface the author says that "eponyms are used freely, for the practice of medicine without eponyms is like the practice of law without trial precedents." However interesting eponyms may be, it seems to me that one is taking things a little far when hemorrhoids are referred to as St. Fiacre's disease.

I believe that the most disappointing part of the work is the bibliography. For some reason the statement "woe be to the gastroenterologist whose mind is a bibliography" appears in the preface. I am not certain what the author means by this, but apparently he uses it as a reason for keeping the bibliography short. The references given are those which were thought to be important by the author. However, there are many notable omissions, such as Ratnoff's and Patek's classic article on cirrhosis and Alvarez's paper on hysterical abdominal ptoptosis. The very brief bibliographies at the end of each chapter do not save space, as additional references could have been added to every chapter except one without increasing the number of pages. For instance, on page 82, at the end of Chapter IV, only eight references are given and the remainder of the bibliography page, amounting to some three-fourths of the writing area, is left blank. I am sure it would have been of help to readers if a larger bibliography had been included.

The book is attractively and sturdily bound, and it is printed on excellent paper in good legible type. The illustrations are numerous and well done, and many representative roentgenograms are included.

I trust that the reader of this review does not conclude from my comments that this is not a worth-while volume, for I mean to convey just the opposite, namely, that this is a good, well written, and, at times, entertaining book on clinical gastroenterology.

JAMES A. CLIFTON, M.D.

Die Lungenarterienbahn bei angeborenen Herzfehlern. Zwanglose Abhandlungen aus dem Gebiet der normalen und pathologischen Anatomie, No. 2 (Edited by Prof. Dr. W. Bargmann and Prof. Dr. W. Doerr, Kiel). By Priv.-Doz. Dr. K. Köhn and Dr. M. Richter, Berlin. Price, single copy, $7; subscription, $5.60. Pp. 112, with 52 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1958.

The changes in the pulmonary vasculature found in congenital and acquired heart disease have long been known. However, with the advent of cardiac surgery our understanding of the processes involved has become a problem of practical importance. Even though an extensive literature on the subject has accumulated, no general consensus of opinion exists as to the etiology of these pulmonary vascular changes, the underlying pathophysiologic mechanisms involved, and the interpretation of the anatomical substrate. This very timely publication is based on the examination of the lungs of forty-one patients with congenital heart disease by the pathologist. A short review of the embryology, anatomy, and physiology of the pulmonary vasculature precedes the description of the microscopic findings of the heart and lungs for each patient.

The histological findings in the lungs are reported in detail and illustrated with black-and-white photomicrographs of good quality and a few schematic drawings. The clinical histories are short and sketchy and are absent in eight of the cases. No hemodynamic data are presented. In the third part, the findings are discussed systematically with an extensive review of the existing world literature, as documented by a bibliography of over five hundred references.

The cases are divided into three groups. Group 1 comprises twenty-one cases with congenital anomalies accompanied by increased pulmonary flow, with or without increased PA pressure and resistance, such as patent ductus arteriosus, interatrial and interventricular septal defects, anomalous pulmonary venous return, Eisenmenger syndrome, and complete transposition of the great vessels.

The seventeen patients in Group 2 represent malformations usually associated with diminished pulmonary flow and normal or low pulmonary artery pressures. They include tetralogy and pentalogy of Fallot, Ebstein's disease with open foramen ovale, pulmonary atresia with patent ductus, and pseudotruncus arteriosus.

There were only three patients in Group 3, all of whom had coarctation of the aorta, representing an anomaly that leaves unaltered the pulmonary flow and pressure.

The age of the patients varied between a few days and seventy years. In a few very young infants, no characteristic changes of the pulmonary vasculature were found. In the remaining patients, four distinct groups of alterations were observed:

1. Changes found particularly in the large and medium-sized pulmonary arteries, which were characterized by hyperplasia of the vessel wall, with fibrosis of the adventia, fibrosis or elastosis of the media, and artheromatous or fibrous intimal thickening. These manifestations of "simple pulmonary artery sclerosis" were seen predominantly in patients in Group 1 with increased PA flow and were age-dependent. The casual relationship of these lesions to altered fluid mechanics, i. e., increased flow pressure and to hypoxemia, are discussed.

2. Alterations particularly of the small arteries, arterioles, and precapillaries, which were manifested by fibrinoid median necrosis, elastolysis, verrucous cellular or fibrous intimal thickening, extensive thrombosis with or without recanalization, and lymphocytic-histiocytic or leukocytic vessel wall infiltrations. These changes were unrelated to age and found equally frequent in Groups 1 and 2, i. e., in patients with very different pulmonary hemodynamics. In view of the presenting morphology and because frequently a rheumatic verrucous endocarditis was also present, the authors interpret these changes as manifestations of a true arteritis on an allergic-rheumatic basis. Their similarity to such entities as "thrombarteritis obliterans Wiese," "thrombarteriopathia pulmonum Bredt," periarteritis nodosa, giant-cell arteritis, and rheumatic arteritis is stressed. Mechanical hemodynamic factors are discussed and believed to act merely by creating a locus minoris resistentiae. Altered O_2 and CO_2 tension is acknowledged as a contributory factor.

3. Changes characterized by fine endothelial septation of the small pulmonary arteries and hemangioma-like vascular conglomerates are described. In the American literature these lesions are usually interpreted as end-stages of recanalized vascular thrombosis. On the basis of their studies, the authors advance the interesting theory that these lesions represent true congenital vascular anomalies.

4. The frequent occurrence and extensive development of vascular anastomoses between bronchial and pulmonary vessels and subpleural giant capillaries are emphasized. In the final analysis the authors stress the multiplicity of factors involved in pulmonary vascular changes in congenital heart disease and the absence of a uniform morphology and pathogenesis.

This monograph is well written, makes for stimulating reading, and presents a systematic review of the subject.

HANS U. WESSEL, M.D.

Spondylitis Ankylopoetica (Morbus Strümpell-Marie-Bechterew). By Prof. Dr. Victor R. Ott and Prof. Dr. Hans Wurm. Price, $9.50. Pp. 246. Dr. Dietrich Steinkopff Verlag, (16) Holzhof-Alee 35, Darmstadt, 1957.

This 246-page paper-bound volume is more than a monograph. It can be used as a textbook dealing with this particular type of arthritis, and it is thoroughly and adequately presented by the two authors. It should be in the library of every specialist in the treatment of arthritic diseases and available as a reference book to every physician who treats arthritis in any of its forms. This is the third book of a series which has been planned under the

direction of Prof. Dr. Rudolf Schoen, Director of Medicine in the University Clinic and Polyclinic in Göttingen, Germany. The title for the entire series of books, of which this is one volume, is "Der Rheumatismus."

There are eighty beautifully reproduced illustrations, including roentgenograms, photomicrographs, and photographs of completely ankylosed spines, which have been prepared by some special technique. Some of these spines were photographed after they were split saggitally, and these photographic illustrations are remarkable in that a single photographic print appears to have three dimensions, as though viewed through a steriopticon.

The authors have discussed in great detail the techniques of correctly diagnosed spondylitis ankylopoetica, and their reproduction of the x-rays is also remarkable because of the clarity and excellence of detail shown in each x-ray print. A detailed discussion of the theories regarding etiology of this crippling, and often deforming, disease is well presented. The authors describe all methods of treating the disease which are known today. Perhaps the most important section in the book is that which describes the pathology and correlates the x-ray findings with microscopic sections of bone, intervertebral disks, and ligaments of the spine. Again, the excellence of these illustrations is deserving of special commendation.

The bibliography fills eleven pages and is the most complete of any that I have seen. This book has been carefully and accurately prepared, and the material is presented concisely and effectively. It should be translated into English and made available to the large group of physicians and surgeons who find the German language difficult.

EDWARD L. COMPERE, M.D.

News and Comment

ANNOUNCEMENTS

Postgraduate Assembly in Endocrinology and Metabolism.—The Tenth Annual Postgraduate Assembly in Endocrinology and Metabolism of the Endocrine Society will take place from Sept. 29 to Oct. 3 at the State University of New York Upstate Medical Center in Syracuse, N. Y.

Thirty-five hours of credit in Category I will be allowed for the course by the American Academy of General Practice. Tuition for the course is $100. Further information can be obtained by writing to Dr. William A. Harris, Dean of Postgraduate Education, State University Upstate Medical Center, 766 Irving Ave., Syracuse 10, N. Y. Registration is limited to 100.

LATEST NUCLEAR RESEARCH IN MEDICINE AVAILABLE

International Conference on Peaceful Uses of Atomic Energy.—The latest research in the application of atomic energy to medicine will be presented at the 1958 International Conference on the Peaceful Uses of Atomic Energy, to be held in Geneva, Sept. 1-13, 1958.

The Document Service of The Chronicle of United Nations Activities has inaugurated a complete service to supply the medical profession with materials of the Conference. Available immediately are the lists of papers to be presented, including several hundred papers dealing with medical research from the major laboratories throughout the world.

Topics covered include uses of isotopes in medicine, including the newer forms of therapy, such as radiocobalt, radiocesium, and other large teletherapy sources; uses of isotopes in human, plant, and animal physiology; biological effects of radiation, including radiation sickness, induction of leukemia and new growths, acceleration of aging, and continuous irradiation of rapidly reproducing populations, e. g., yeasts and flies, with reference to genetic problems.

These lists may be obtained free by writing to Document Service, Department PM, The Chronicle of United Nations Activities, 234 W. 26th St., New York 1.

Laboratory Refresher Training Courses.—The following is the schedule of laboratory refresher training courses sponsored by the Department of Health, Education, and Welfare, Public Health Service, Bureau of State Services, Communicable Disease Center, Laboratory Branch, Chamblee, Ga., from July, 1958, to June, 1959.

Location of classrooms is indicated as follows: 1, Bldg. 27, Chamblee, Ga.; 2, Bldg. 30, Chamblee, Ga.; 3, Virus Laboratory, Montgomery, Ala. Courses given by special arrangement only are indicated by * under the date.

Date	Course No.	Courses	Duration Wk.	Location
Sept. 15-Oct. 10	8.00	Laboratory Methods in the Diagnosis of Parasitic Diseases Part 1. Intestinal Parasites	4	1
Oct. 6-10	8.26	Laboratory Methods in the Diagnosis of Rabies	1	2
Oct. 13-24	8.20	Laboratory Methods in the Diagnosis of Viral and Rickettsial Diseases	2	3
Oct. 13-31	8.01	Laboratory Methods in the Diagnosis of Parasitic Diseases Part 2. Blood Parasites	3	1
Oct. 20-31	8.55	Laboratory Methods in the Diagnosis of Tuberculosis	2	2
Jan. 5-30	8.15	Laboratory Methods in Medical Mycology Cutaneous, Subcutaneous and Systemic Fungi	4	1
Jan. 12-16	8.26	Laboratory Methods in the Diagnosis of Rabies	1	2
Jan. 26-Feb. 6	8.55	Laboratory Methods in the Diagnosis of Tuberculosis	2	2
Feb. 9-20	8.17	Laboratory Methods in the Study of Pulmonary Mycoses	2	1

Date	Course No.	Courses	Duration Wk.	Location
Mar. 2-6	9.40	Laboratory Diagnostic Methods in Veterinary Mycology	1	1
Mar. 2-13	8.40	Laboratory Methods in the Diagnosis of Bacterial Diseases Part 1. General Bacteriology	2	2
Mar. 9-20	8.20	Laboratory Methods in the Diagnosis of Viral and Rickettsial Diseases	2	3
Mar. 16-27	8.41	Laboratory Methods in the Diagnosis of Bacterial Diseases Part 2. General Bacteriology	2	2
Mar. 16-Apr. 3	9.41	Serologic Methods in Microbiology	3	1
Mar. 30-Apr. 10	8.50	Laboratory Methods in the Diagnosis of Bacterial Diseases, Enteric Bacteriology	2	2
*	8.05	Laboratory Methods in the Diagnosis of Malaria	2	1
*	8.21	Special Training in Virus Techniques	2-4	3
*	8.42	Typing of Corynebacterium Diphtheriae	1	2
*	8.51	Special Problems in Enteric Bacteriology	2	2
*	8.52	Phage Typing of Salmonella Typhosa	1	2
*	8.53	Laboratory Methods in the Diagnosis of Leptospirosis	1-4	2
*	8.54	Serologic Differentiation of Streptococci	2	2
*	8.56	Bacteriophage Typing of Staphylococci	2	2

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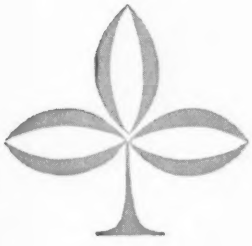
ENS 
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1. Reeves, R. J.: Southern M. J. 50:1377 (Nov.) 1957.
2. Shehadi, W. H.: Am. J. Gastroenterol. 28:236 (Sept.) 1957.

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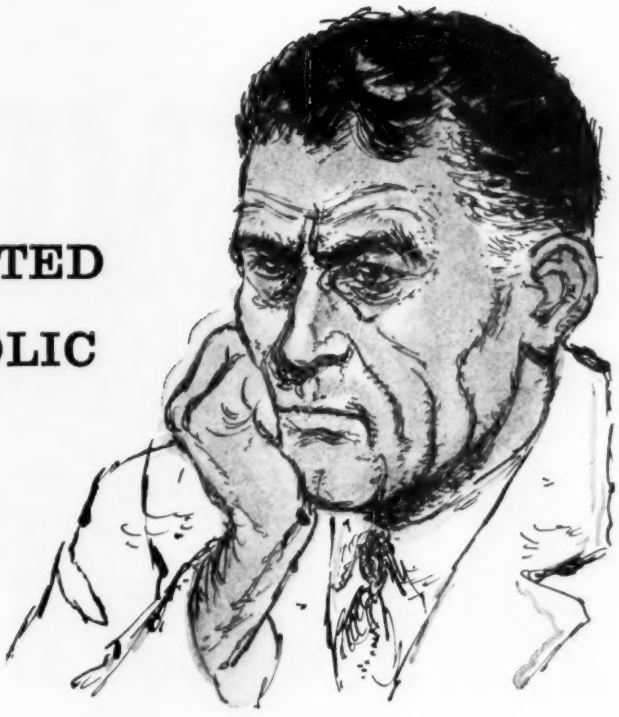

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*Smith, J.A.: *J.A.M.A.* 152:384, May 30, 1953. Brown, W.T., and Smith, J.A.: *South. M. J.* 46:582, June, 1953. Smith, J.A.: *Postgrad. Med.* 16:316, Oct., 1954. McCullagh, W.H.: *J. Florida M.A.* 41:718, Mar., 1955.

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1. *Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Card.* **1**:395, *March 1958.*
2. *Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology* **8**:504, *Dec. 1957.*

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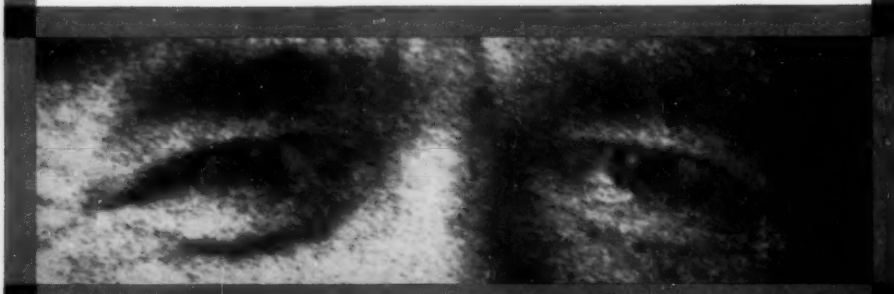

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Source—Hyman, M.: Some Aspects of Psychiatry in General Practice, GP *16*:83 (Oct.) 1957.

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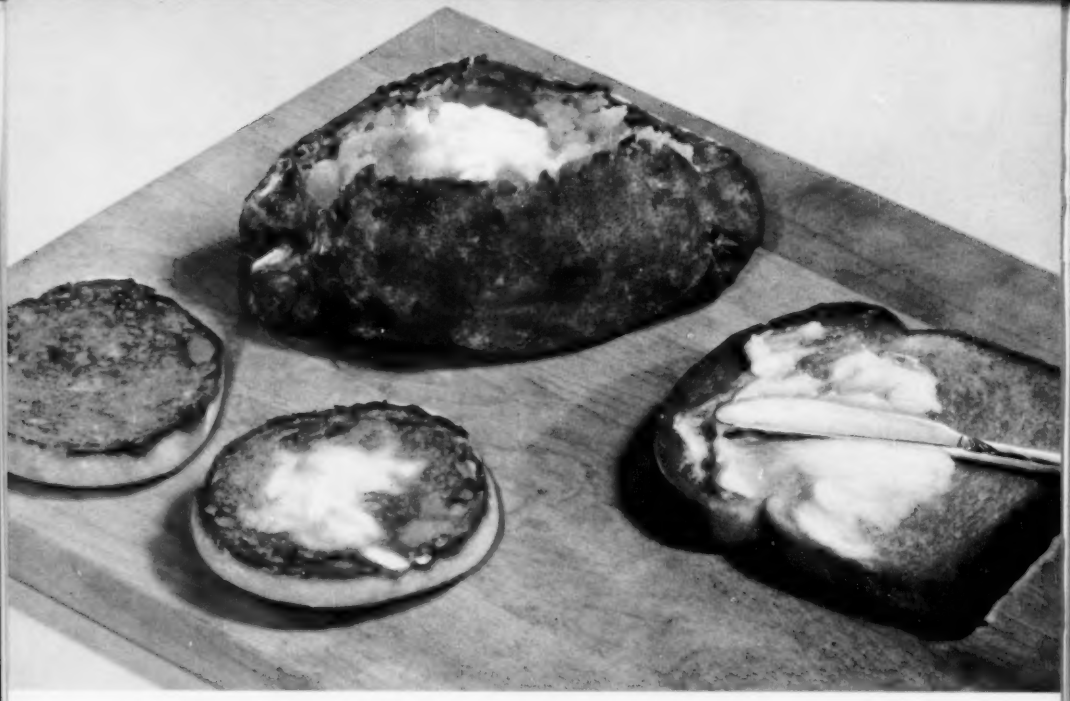

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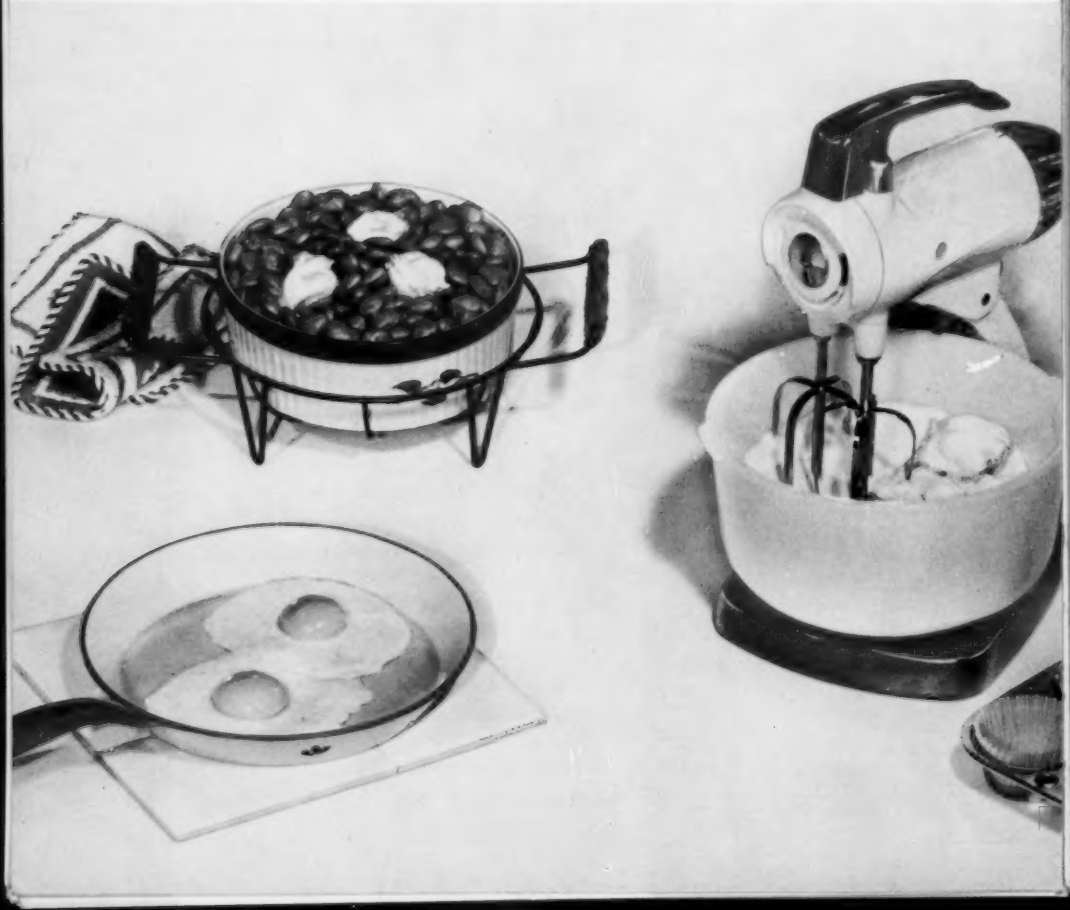

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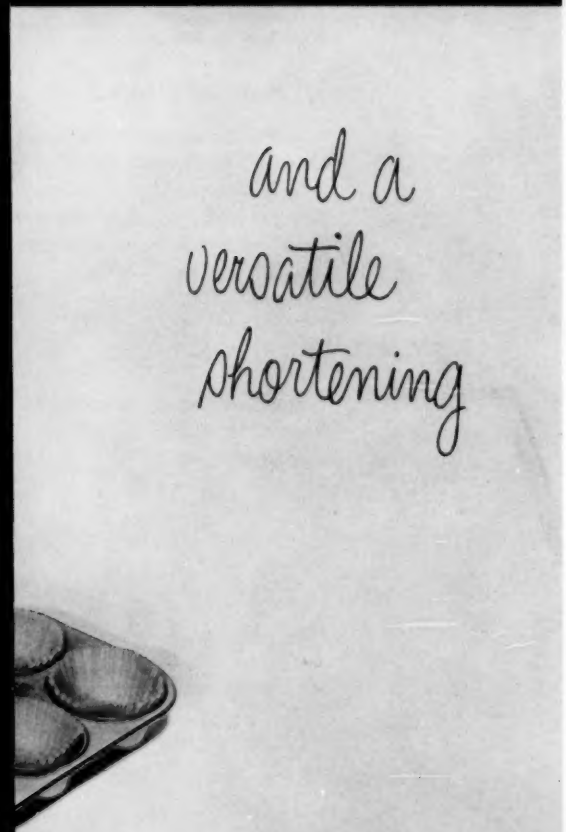

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